

U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (REV. 11-2000)		ATTORNEY'S DOCKET NUMBER Le A 33 846
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO (If known, see 37 CFR 1.5) 10/019007
INTERNATIONAL APPLICATION NO. PCT/EP00/05410	INTERNATIONAL FILING DATE 13 June 2000 (13.06.00)	PRIORITY DATE CLAIMED 25 June 1999 (25.06.99)
TITLE OF INVENTION COMBINATION OF MTIP INHIBITORS AND HMG-CoA REDUCTASE INHIBITORS AND THE USE THEREOF IN MEDICAMENTS		
APPLICANT(S) FOR DO/EO/US GRUTZMANN, et al.		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
<p>1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.</p> <p>2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.</p> <p>3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.</p> <p>4. <input checked="" type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31).</p> <p>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</p> <p>6. <input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input checked="" type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4).</p> <p>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made.</p> <p>8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</p> <p>9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</p> <p>10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).</p>		
<p>Items 11 to 20 below concern document(s) or information included:</p> <p>11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</p> <p>12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</p> <p>13. <input checked="" type="checkbox"/> A FIRST preliminary amendment.</p> <p>14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.</p> <p>15. <input type="checkbox"/> A substitute specification.</p> <p>16. <input type="checkbox"/> A change of power of attorney and/or address letter.</p> <p>17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.</p> <p>18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4).</p> <p>19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).</p> <p>20. <input checked="" type="checkbox"/> Other items or information: 1) Certificate of Mailing under 37 C.F.R. 1.10; 2) Transmittal of Information Disclosure Statement under 37 C.F.R. 1.97(b); 3) Information Disclosure Citation (Modified Form PTO-1449) and references cited therein 4) Return Receipt Postcard.</p>		
<p>Date of Deposit: DEC 21 2001</p> <p>Express Mail Label No.: ET386113230US</p>		

U.S. APPLICATION NO. (if known; see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO PCT/EP00/05410	ATTORNEY'S DOCKET NUMBER Le A 33 846																							
21. <input checked="" type="checkbox"/> The following fees are submitted:		CALCULATIONS PTO USE ONLY																							
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):																									
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.....		\$1000.00																							
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO		\$860.00																							
		\$890.00																							
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO		\$710.00																							
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)		\$690.00																							
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)		\$100.00																							
ENTER APPROPRIATE BASIC FEE AMOUNT =		\$ 890.00																							
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		\$																							
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">CLAIMS</th> <th style="width: 25%;">NUMBER FILED</th> <th style="width: 25%;">NUMBER EXTRA</th> <th style="width: 25%;">RATE</th> </tr> </thead> <tbody> <tr> <td>Total claims</td> <td>12 - 20 =</td> <td>0</td> <td>x \$18.00</td> </tr> <tr> <td>Independent claims</td> <td>3 - 3 =</td> <td>0</td> <td>x \$80.00</td> </tr> <tr> <td colspan="2">MULTIPLE DEPENDENT CLAIM(S) (if applicable)</td> <td>0</td> <td>+ \$270.00</td> </tr> <tr> <td colspan="2"></td> <td></td> <td>280.00</td> </tr> <tr> <td colspan="2" style="text-align: center;">TOTAL OF ABOVE CALCULATIONS =</td> <td style="text-align: right;">\$ 890.00</td> </tr> </tbody> </table>		CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	Total claims	12 - 20 =	0	x \$18.00	Independent claims	3 - 3 =	0	x \$80.00	MULTIPLE DEPENDENT CLAIM(S) (if applicable)		0	+ \$270.00				280.00	TOTAL OF ABOVE CALCULATIONS =		\$ 890.00	\$
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE																						
Total claims	12 - 20 =	0	x \$18.00																						
Independent claims	3 - 3 =	0	x \$80.00																						
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		0	+ \$270.00																						
			280.00																						
TOTAL OF ABOVE CALCULATIONS =		\$ 890.00																							
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.		+																							
SUBTOTAL =		\$ 890.00																							
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).		\$																							
TOTAL NATIONAL FEE =		\$ 890.00																							
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property		+																							
TOTAL FEES ENCLOSED =		\$ 890.00																							
		Amount to be refunded: \$																							
		charged: \$																							

a. A check in the amount of \$ _____ to cover the above fees is enclosed.

b. Please charge my Deposit Account No. **13-3372** in the amount of \$ **890.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

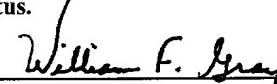
c. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **13-3372**. A duplicate copy of this sheet is enclosed.

d. Fees are to be charged to a credit card. **WARNING: Information on this form may become public. Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Jeffrey M. Greenman
Vice President, Patents and Licensing
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516


 SIGNATURE
William F. Gray
 NAME
31,018
 REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Grutzmann, et al.

Group Art Unit:

Serial No: National Stage Filing of PCT/EP00/05410 Examiner:

Filed: Herewith

For: Combination of MTP Inhibitors and HMG-CoA Reductase Inhibitors and the Use
Thereof in Medicaments

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents

Washington, DC 20231

Sir:

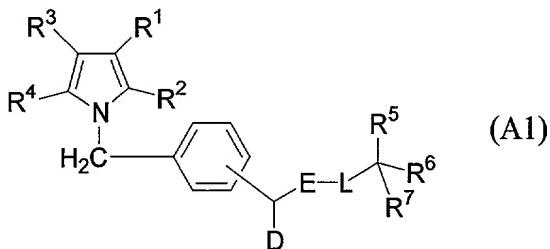
This preliminary amendment is submitted in the above-identified national stage application of PCT/EP00/05410 filed on even date herewith.

Please amend the above-identified application as follows:

In the claims:

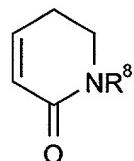
Please amend claims 1-12 as shown below:

1. (Amended) A method for the prophylaxis or treatment of cardiovascular diseases which comprises administering an effective amount of a combination of component A and component B, component A being at least one MTP inhibitor [as component A] of the general formula (A1)



in which

R^1 and R^2 , including the double bond connecting them, together form a phenyl or pyridyl ring or a ring of the formula



in which

R^8 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^3 and R^4 , including the double bond connecting them, together form a phenyl ring or a 4- to 8-membered cycloalkene or oxocycloalkene radical,

all ring systems mentioned under R^1/R^2 and R^3/R^4 optionally being substituted up to 3 times, identically or differently, by halogen, trifluoromethyl, carboxyl, hydroxyl, by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

D represents hydrogen, cycloalkyl having 4 to 12 carbon atoms or straight-chain or

branched alkyl having up to 12 carbon atoms,

E represents the -CO- or -CS- group,

L represents an oxygen or sulphur atom or a group of the formula -NR⁹,

in which

R⁹ denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or phenyl,

R⁵ denotes phenyl or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O,

the cyclic systems optionally being substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxy carbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

and/or the cyclic systems optionally being substituted by a group of the formula -OR¹⁰ or -NR¹¹R¹²,

in which

R¹⁰ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

R¹¹ and R¹² are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms or straight-chain or branched acyl having up to 8 carbon atoms, which is optionally substituted by a group of the formula -NR¹³R¹⁴,

in which

R¹³ and R¹⁴ are identical or different and denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

R⁶ represents hydrogen, carboxyl or straight-chain or branched alkoxy carbonyl having up to 5 carbon atoms, or represents straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or by a group of the formula -O-CO-R¹⁵,

in which

R¹⁵ denotes phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl or by straight-chain or branched alkyl having up to 5 carbon atoms, or denotes straight-chain or branched alkyl or alkenyl each having up to 22 carbon atoms, each of which is optionally substituted by a group of the formula -OR¹⁶,

in which

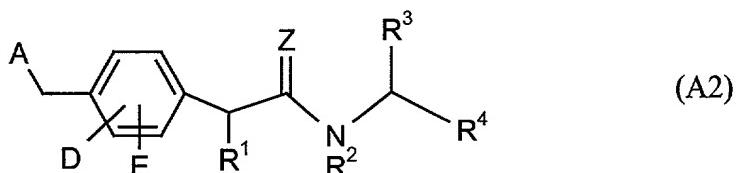
R¹⁶ denotes hydrogen, benzyl, triphenylmethyl or straight-chain or

branched acyl having up to 6 carbon atoms,

R^7 represents hydrogen or

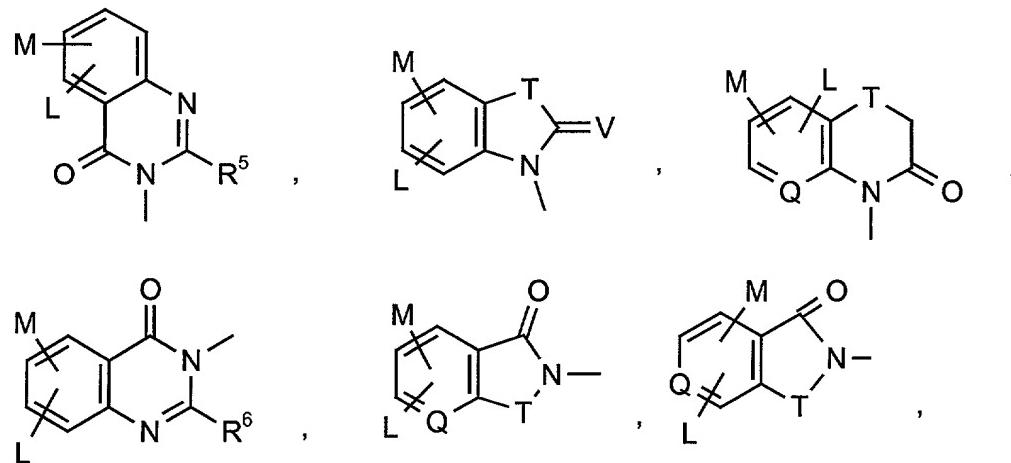
R^6 and R^7 together represent the group of the formula $=O$,

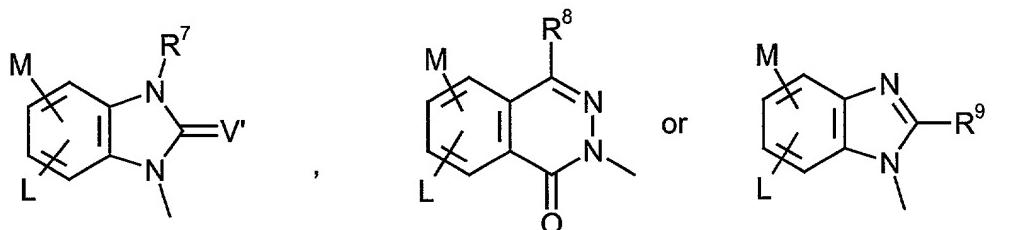
or of the general formula (A2)



in which

A represents a radical of the formula





in which

L and M are identical or different and

denote hydrogen, halogen, trifluoromethyl, carboxyl, cycloalkyl having 3 to 6 carbon atoms, hydroxyl, phenyl or straight-chain or branched alkyl, alkoxy carbonyl or alkoxy each having up to 6 carbon atoms,

Q denotes a nitrogen atom or the -CH- group,

T denotes a group of the formula -SO₂ or -CO or an oxygen or sulphur atom,

V denotes an oxygen or sulphur atom,

R⁵, R⁶, R⁷ and R⁸ are identical or different and

denote hydrogen, or straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, each of which is optionally substituted by halogen or by straight-chain or branched alkyl having up to 6 carbon atoms,

R⁹ denotes trifluoromethyl, benzyl or a 5- to 7-membered, optionally benzofused heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, which is optionally substituted up to 3 times, identically or differently, by halogen, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms, or

denotes a group of the formula -S(O)_a-R¹⁰,

in which

a denotes a number 0, 1 or 2,

R¹⁰ denotes straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by straight-chain or branched acyl having up to 6 carbon atoms or by aryl or aroyl each having up to 10 carbon atoms, which for their part can be substituted up to 2 times, identically or differently, by halogen, trifluoromethyl or by straight-chain or branched acyl having up to 5 carbon atoms, or denotes aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, hydroxyl, trifluoromethyl or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms,

D and E are identical or different and

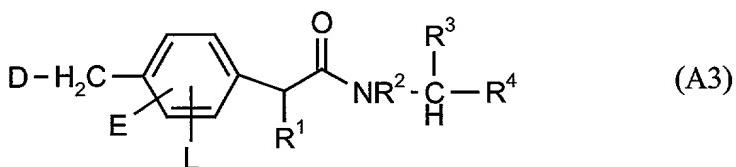
represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

Z represents an oxygen or sulphur atom,

R¹ represents cycloalkyl having 3 to 10 carbon atoms or straight-chain or branched alkyl having 1 to 10 carbon atoms, or represents phenyl which is optionally substituted up to 2 times, identically or differently, by halogen, nitro, cyano, hydroxyl, straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

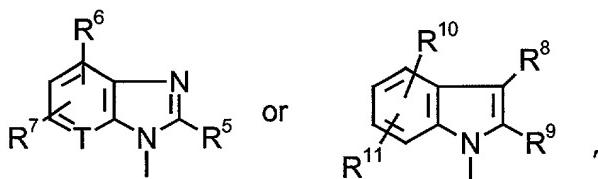
- R² represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,
- R³ represents hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or
represents cycloalkyl having 3 to 7 carbon atoms, or
represents phenyl or a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, each of which is optionally substituted up to 3 times, identically or differently, by halogen, nitro, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having up to 6 carbon atoms,
- R⁴ represents hydrogen or a group of the formula -CH₂-OH or CH₂O-CO-R¹¹,
in which
- R¹¹ denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms or phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl, cyano or straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

or of the general formula (A3)



in which

D represents a radical of the formula



in which

T denotes a nitrogen atom or the -CH- group,

R⁶, R⁷, R¹⁰ and R¹¹ are identical or different and

denote hydrogen, trifluoromethyl, halogen or straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms,

R⁵, R⁸ and R⁹ are identical or different and

denote hydrogen, cycloalkyl having 3 to 6 carbon atoms, phenyl, straight-chain or branched alkoxycarbonyl having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by halogen,

or, if T represents a nitrogen atom, R⁵ can also denote benzyl,

E and L are identical or different and

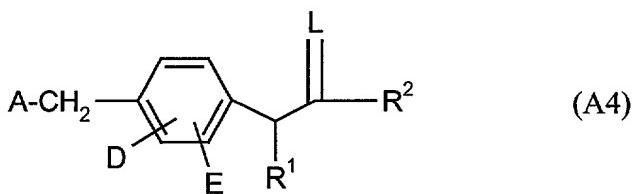
represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

- R¹ represents cycloalkyl having 3 to 10 carbon atoms or straight-chain or branched alkyl having 1 to 10 carbon atoms, or represents phenyl which is optionally substituted up to 2 times, identically or differently, by halogen, cyano, hydroxyl, straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,
- R² represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,
- R³ represents hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or represents cycloalkyl having 3 to 7 carbon atoms, or represents phenyl or a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, each of which is optionally substituted up to 3 times, identically or differently, by halogen, nitro, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having up to 6 carbon atoms,
- R⁴ represents hydrogen or a group of the formula -CH₂-OH or CH₂O-CO-R¹²,

in which

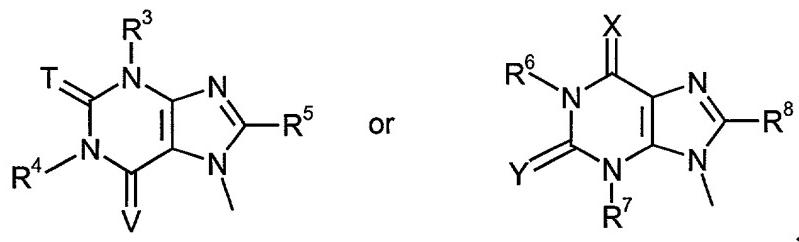
R¹² denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms or phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl, cyano or straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

or of the general formula (A4)



in which

A represents a radical of the formula



in which

R³, *R⁴*, *R⁶* and *R⁷* are identical or different and

denote hydrogen, cycloalkyl having 3 to 7 carbon atoms or aryl having 6 to 10 carbon atoms,

or denote straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by halogen, hydroxyl or aryl having 6 to 10 carbon atoms,

T, *V*, *X* and *Y* are identical or different and denote an oxygen or sulphur atom,

R⁵ and *R⁸* are identical or different and

denote hydrogen, halogen, cycloalkyl having 3 to 8 carbon atoms or

100-19000-112-104

straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by cycloalkyl having 3 to 8 carbon atoms, or by a 5- to 6-membered, aromatic, optionally benzo-fused heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, or by aryl having 6 to 10 carbon atoms, where the cyclic systems for their part can be substituted up to 3 times, identically or differently, by a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, or by phenyl, benzyl, halogen, hydroxyl, carboxyl or by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms, or denote aryl having 6 to 10 carbon atoms or a 5- to 7-membered aromatic, optionally benzo-fused heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, each of which is optionally substituted up to 3 times, identically or differently, by halogen, phenyl, trifluoromethyl, hydroxyl, carboxyl or by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or by a group of the formula -(CO)_a-NR⁹R¹⁰,

in which

a denotes a number 0 or 1,

R⁹ and R¹⁰ are identical or different and

denote hydrogen, phenyl or straight-chain or branched alkyl or acyl each having up to 5 carbon atoms,

D and E are identical or different and

represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-chain

or branched alkyl, alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

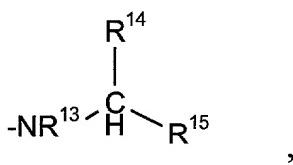
R¹ represents hydrogen or cycloalkyl having 3 to 8 carbon atoms, or
 represents straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms, phenyl or by a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, or
 represents phenyl or a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, the ring systems optionally being substituted up to 3 times, identically or differently, by halogen, phenyl, trifluoromethyl or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms, hydroxyl or by a group of the formula -NR¹¹R¹²,

in which

R¹¹ and R¹² have the meaning of R⁹ and R¹⁰ indicated above and are identical to or different from this,

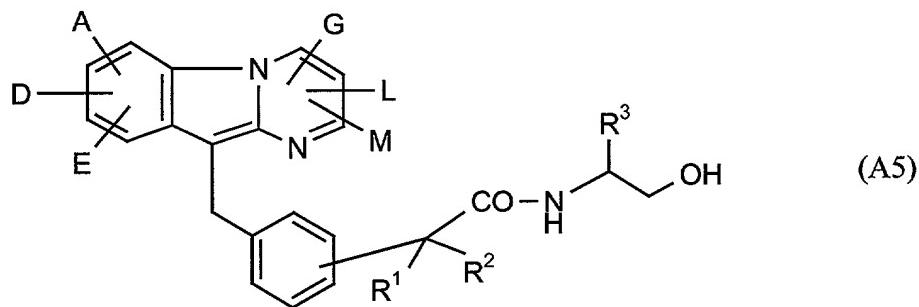
L represents an oxygen or sulphur atom,

R² represents mercapto, hydroxyl, straight-chain or branched alkoxy having up to 8 carbon atoms or the group of the formula



in which

- R¹³ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,
- R¹⁴ denotes hydrogen, phenyl or a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O,
- R¹⁵ denotes hydrogen or straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by hydroxyl,
or of the general formula (A5)



in which

A, D, E, G, L and M are identical or different and represent hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

R¹ and R² are identical or different and

represent hydrogen, cycloalkyl having 3 to 8 carbon atoms or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms or
represent phenyl which is optionally substituted by halogen or trifluoromethyl, or

R¹ and R², together with the carbon atom, form a 4- to 8-membered cycloalkyl ring

and

R³ represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxycarbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

and/or is optionally substituted by a group of the formula -OR⁴ or -NR⁵R⁶,

in which

R⁴ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

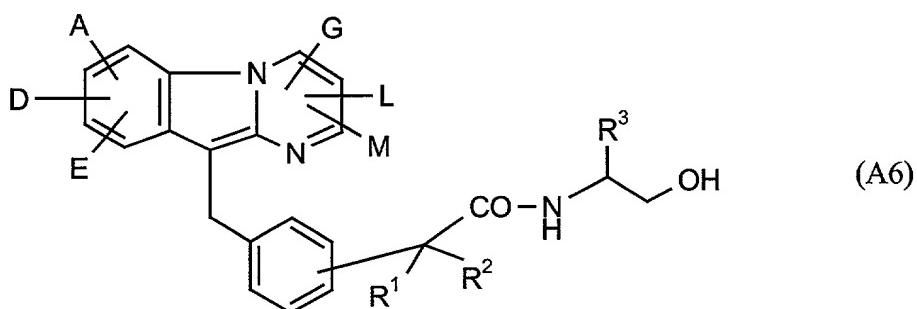
R⁵ and R⁶ are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,
or denote straight-chain or branched acyl having up to 8 carbon atoms,
which is optionally substituted by a group of the formula -NR⁷R⁸,

in which

R^7 and R^8 are identical or different and

denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

or of the general formula (A6)



in which

A, D, E, G, L and M are identical or different and

represent hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

R^1 and R^2 are identical or different and

represent hydrogen, cycloalkyl having 3 to 8 carbon atoms or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms, or

represent phenyl which is optionally substituted by halogen or trifluoromethyl, or

R¹ and R², together with the carbon atom, form a 4- to 8-membered cycloalkyl ring

and

R³ represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxycarbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

and/or is optionally substituted by a group of the formula -OR⁴ or -NR⁵R⁶,

in which

R⁴ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

R⁵ and R⁶ are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,
or denote straight-chain or branched acyl having up to 8 carbon atoms,
which is optionally substituted by a group of the formula -NR⁷R⁸,

in which

R⁷ and R⁸ are identical or different and
denote hydrogen or straight-chain or branched acyl having up to
8 carbon atoms,

if appropriate in an isomeric form and their salts

and component B being at least one HMG-CoA reductase inhibitor.

2. (Amended) The method according to Claim 1 wherein said cardiovascular diseases are associated with metabolic diseases or deficits.
3. (Amended) The method according to Claim 2 for the control of arteriosclerosis, diseases of the coronary vessels of the heart, raised serum lipids, hypercholesterolaemia, hypertriglyceridaemia and mixed forms which are combined with raised VLDL or LDL and/or raised chylomicrons, and of syndrome X.
4. (Amended) The method according to Claim 2 for the treatment of secondary hypercholesterolaemia and secondary hypertriglyceridaemia, which are optionally associated with apolipoprotein E polymorphism, obesity, chylomicronaemia and chylomicronaemia syndrome, renal insufficiency, chronic renal insufficiency, nephrotic syndrome, diabetes mellitus type II, and with hepatomas and plasmacytomas.
5. (Amended) The method according to Claim 2, characterized in that component A is a compound of the general formula (A1).
6. (Amended) The method according to Claim 2, characterized in that component A is a compound of Examples 1-119.
7. (Amended) The method according to Claim 2, characterized in that component A is a compound of Examples 92-119.

- Preliminary
Amendment
8. (Amended) The method according to Claim 2, characterized in that component A is a compound of Examples 48 or 80.
 9. (Amended) A pharmaceutical composition comprising a combination of an MTP inhibitor as component A and an HMG-CoA reductase inhibitor as component B according to Claim 1 and, if appropriate, one or more further suitable components.
 10. (Amended) A pharmaceutical composition according to Claim 9, characterized in that it contains, as component A, the active compound 2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide or 2-cyclopentyl-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide and, as component B, the active compound atorvastatin, cerivastatin, simvastatin, pravastatin, lovastatin, fluvastatin, itavastatin or ZD 4522.
 11. (Amended) A pharmaceutical composition according to Claim 9, characterized in that it contains, as component A, the compound (2S)-2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-(1R)-hydroxy-1-phenyl-ethyl)-acetamide.
 12. (Amended) A process for the production of a pharmaceutical composition according to Claim 9, characterized in that the components A and B are converted into a suitable administration form with excipients and vehicles and, if appropriate, with further components.

Remarks / Explanations

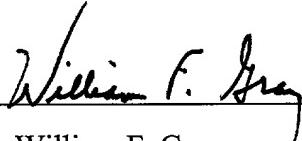
As a result of this preliminary amendment, claims 1-12 are pending in the application. No new matter has been added.

The amendment to structure (A1) in claim 1 is to clarify the drawing. Swiss-type use claims 1-8 have been converted into method of treatment claims. Claims 9-11 now refer to pharmaceutical compositions rather than medicaments. Claim 12 now refers to a process for preparing the pharmaceutical composition.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

In view of the above amendments and explanations, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,



William F. Gray

Bayer Corporation

400 Morgan Lane

West Haven, CT 06516-4175

Reg. No. 31018

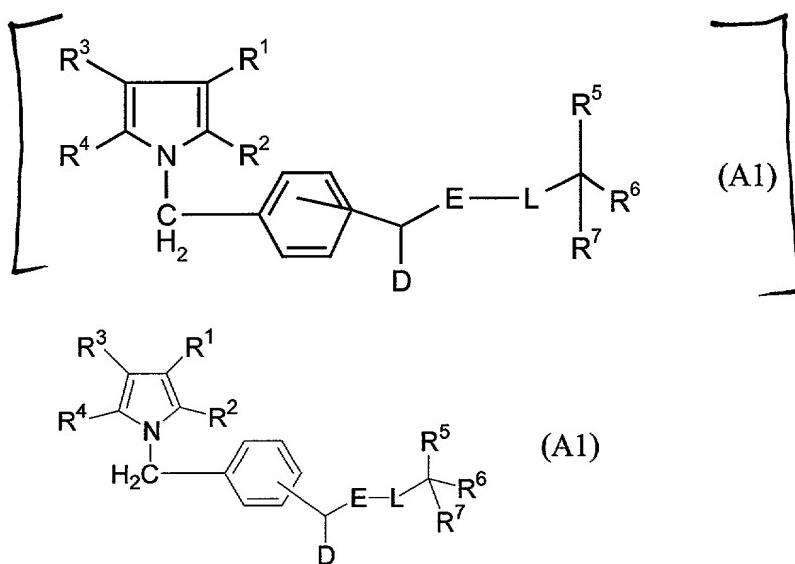
Phone: (203) 812-2712

Date: 20 Dec '01

Version with markings to show changes made:In the claims:

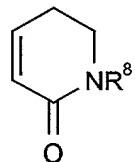
Claims 1-12 have been amended as shown below:

1. (Amended) [Use of] A method for the prophylaxis or treatment of cardiovascular diseases which comprises administering an effective amount of a combination of component A and component B, component A being at least one MTP inhibitor [as component A] of the general formula (A1)



in which

R¹ and R², including the double bond connecting them, together form a phenyl or pyridyl ring or a ring of the formula



in which

- R⁸ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,
- R³ and R⁴, including the double bond connecting them, together form a phenyl ring or a 4- to 8-membered cycloalkene or oxocycloalkene radical,
- all ring systems mentioned under R¹/R² and R³/R⁴ optionally being substituted up to 3 times, identically or differently, by halogen, trifluoromethyl, carboxyl, hydroxyl, by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,
- D represents hydrogen, cycloalkyl having 4 to 12 carbon atoms or straight-chain or branched alkyl having up to 12 carbon atoms,
- E represents the -CO- or -CS- group,
- L represents an oxygen or sulphur atom or a group of the formula -NR⁹,

in which

- R⁹ denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or phenyl,
- R⁵ denotes phenyl or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O,

the cyclic systems optionally being substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxycarbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

and/or the cyclic systems optionally being substituted by a group of the formula -OR¹⁰ or -NR¹¹R¹²,

in which

R¹⁰ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

R¹¹ and R¹² are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms or straight-chain or branched acyl having up to 8 carbon atoms, which is optionally substituted by a group of the formula -NR¹³R¹⁴,

in which

R¹³ and R¹⁴ are identical or different and denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

R⁶ represents hydrogen, carboxyl or straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms,

or represents straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or by a group of the formula -O-CO-R¹⁵,

in which

R¹⁵ denotes phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl or by straight-chain or branched alkyl having up to 5 carbon atoms,
 or denotes straight-chain or branched alkyl or alkenyl each having up to 22 carbon atoms, each of which is optionally substituted by a group of the formula -OR¹⁶,

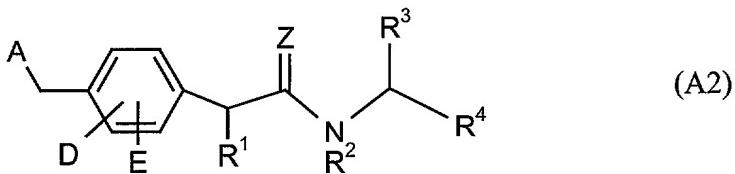
in which

R¹⁶ denotes hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 6 carbon atoms,

R⁷ represents hydrogen or

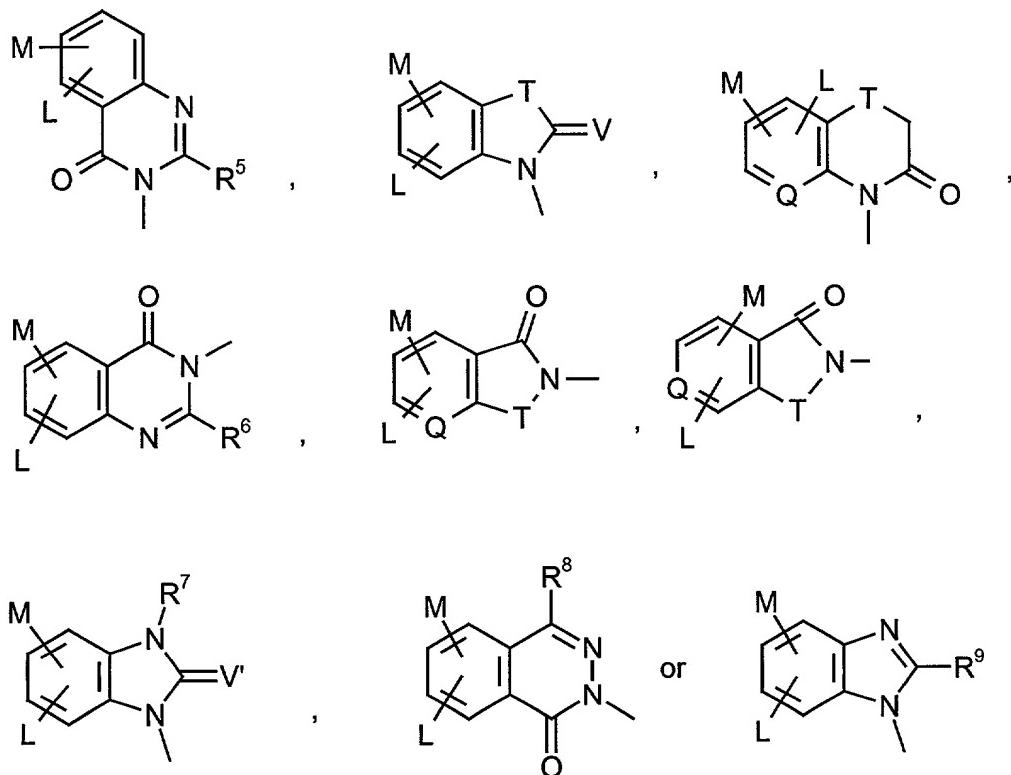
R⁶ and R⁷ together represent the group of the formula =O,

or of the general formula (A2)



in which

A represents a radical of the formula



in which

L and M are identical or different and

denote hydrogen, halogen, trifluoromethyl, carboxyl, cycloalkyl having 3 to 6 carbon atoms, hydroxyl, phenyl or straight-chain or branched alkyl, alkoxy carbonyl or alkoxy each having up to 6 carbon atoms,

Q denotes a nitrogen atom or the -CH- group,

T denotes a group of the formula -SO₂ or -CO or an oxygen or sulphur atom,

V denotes an oxygen or sulphur atom,

R⁵, R⁶, R⁷ and R⁸ are identical or different and

denote hydrogen, or straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, each of which is optionally substituted by halogen or by straight-chain or branched alkyl having up to 6 carbon atoms,

R⁹ denotes trifluoromethyl, benzyl or a 5- to 7-membered, optionally benzo-fused heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, which is optionally substituted up to 3 times, identically or differently, by halogen, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms, or
denotes a group of the formula -S(O)_a-R¹⁰,

in which

a denotes a number 0, 1 or 2,

R¹⁰ denotes straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by straight-chain or branched acyl having up to 6 carbon atoms or by aryl or aroyl each having up to 10 carbon atoms, which for their part can be substituted up to 2 times, identically or differently, by halogen, trifluoromethyl or by straight-chain or branched acyl having up to 5 carbon atoms, or
denotes aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, hydroxyl, trifluoromethyl or straight-chain

or branched alkyl or alkoxy each having up to 5 carbon atoms,

D and E are identical or different and

represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

Z represents an oxygen or sulphur atom,

R¹ represents cycloalkyl having 3 to 10 carbon atoms or straight-chain or branched alkyl having 1 to 10 carbon atoms, or represents phenyl which is optionally substituted up to 2 times, identically or differently, by halogen, nitro, cyano, hydroxyl, straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

R² represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

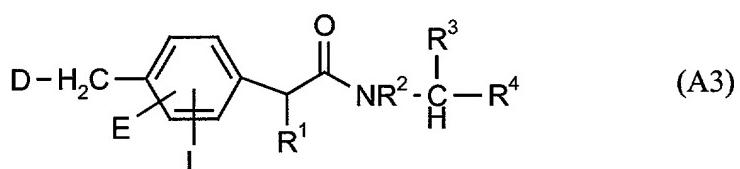
R³ represents hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or represents cycloalkyl having 3 to 7 carbon atoms, or represents phenyl or a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, each of which is optionally substituted up to 3 times, identically or differently, by halogen, nitro, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having up to 6 carbon atoms,

R⁴ represents hydrogen or a group of the formula -CH₂-OH or CH₂O-CO-R¹¹,

in which

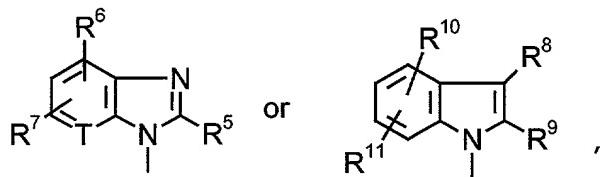
R^{11} denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms or phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl, cyano or straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

or of the general formula (A3)



in which

D represents a radical of the formula



in which

T denotes a nitrogen atom or the -CH- group,

R^6 , R^7 , R^{10} and R^{11} are identical or different and

denote hydrogen, trifluoromethyl, halogen or straight-chain or branched

alkyl or alkoxy each having up to 6 carbon atoms,

R⁵, R⁸ and R⁹ are identical or different and

denote hydrogen, cycloalkyl having 3 to 6 carbon atoms, phenyl, straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by halogen,

or, if T represents a nitrogen atom, R⁵ can also denote benzyl,

E and L are identical or different and

represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

R¹ represents cycloalkyl having 3 to 10 carbon atoms or straight-chain or branched alkyl having 1 to 10 carbon atoms, or represents phenyl which is optionally substituted up to 2 times, identically or differently, by halogen, cyano, hydroxyl, straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

R² represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R³ represents hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or represents cycloalkyl having 3 to 7 carbon atoms, or represents phenyl or a 5- to 7-membered aromatic heterocycle having up to

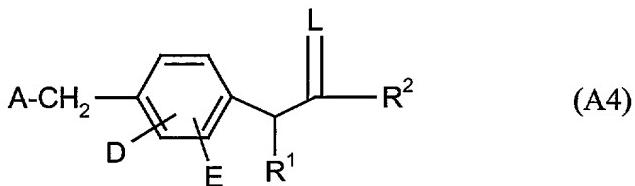
3 heteroatoms from the group consisting of S, N and/or O, each of which is optionally substituted up to 3 times, identically or differently, by halogen, nitro, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having up to 6 carbon atoms,

R^4 represents hydrogen or a group of the formula $-CH_2-OH$ or $CH_2O-CO-R^{12}$,

in which

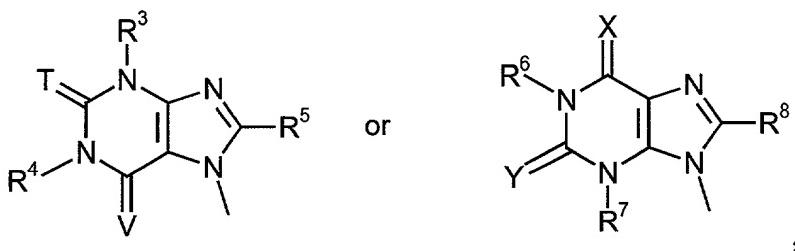
R^{12} denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms or phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl, cyano or straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

or of the general formula (A4)



in which

A represents a radical of the formula



in which

R^3 , R^4 , R^6 and R^7 are identical or different and

denote hydrogen, cycloalkyl having 3 to 7 carbon atoms or aryl having 6 to 10 carbon atoms,

or denote straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by halogen, hydroxyl or aryl having 6 to 10 carbon atoms,

T , V , X and Y are identical or different and denote an oxygen or sulphur atom,

R^5 and R^8 are identical or different and

denote hydrogen, halogen, cycloalkyl having 3 to 8 carbon atoms or straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by cycloalkyl having 3 to 8 carbon atoms, or by a 5- to 6-membered, aromatic, optionally benzofused heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, or by aryl having 6 to 10 carbon atoms, where the cyclic systems for their part can be substituted up to 3 times, identically or differently, by a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, or by phenyl, benzyl, halogen, hydroxyl, carboxyl or by straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 6 carbon atoms, or

denote aryl having 6 to 10 carbon atoms or a 5- to 7-membered aromatic, optionally benzo-fused heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, each of which is optionally substituted up to 3 times, identically or differently, by halogen, phenyl, trifluoromethyl, hydroxyl, carboxyl or by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or by a group of the formula -(CO)_a-NR⁹R¹⁰,

in which

a denotes a number 0 or 1,

R⁹ and R¹⁰ are identical or different and

denote hydrogen, phenyl or straight-chain or branched alkyl or acyl each having up to 5 carbon atoms,

D and E are identical or different and

represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

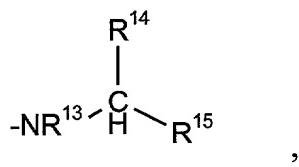
R¹ represents hydrogen or cycloalkyl having 3 to 8 carbon atoms, or represents straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms, phenyl or by a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, or represents phenyl or a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, the ring systems optionally being substituted up to 3 times, identically or differently, by halogen,

phenyl, trifluoromethyl or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms, hydroxyl or by a group of the formula -NR¹¹R¹²,

in which

R¹¹ and R¹² have the meaning of R⁹ and R¹⁰ indicated above and are identical to or different from this,

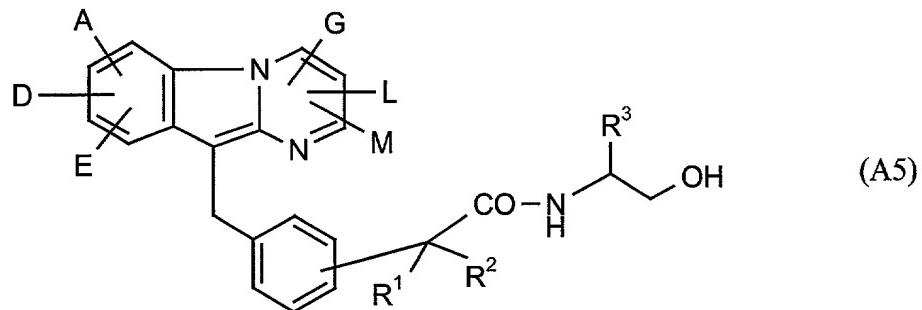
- L represents an oxygen or sulphur atom,
- R² represents mercapto, hydroxyl, straight-chain or branched alkoxy having up to 8 carbon atoms or the group of the formula



in which

- R¹³ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,
- R¹⁴ denotes hydrogen, phenyl or a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O,
- R¹⁵ denotes hydrogen or straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by hydroxyl,

or of the general formula (A5)



in which

A, D, E, G, L and M are identical or different and

represent hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

R¹ and R² are identical or different and

represent hydrogen, cycloalkyl having 3 to 8 carbon atoms or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms or represent phenyl which is optionally substituted by halogen or trifluoromethyl, or

R¹ and R², together with the carbon atom, form a 4- to 8-membered cycloalkyl ring

and

R³ represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxy carbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,
and/or is optionally substituted by a group of the formula -OR⁴ or -NR⁵R⁶,

in which

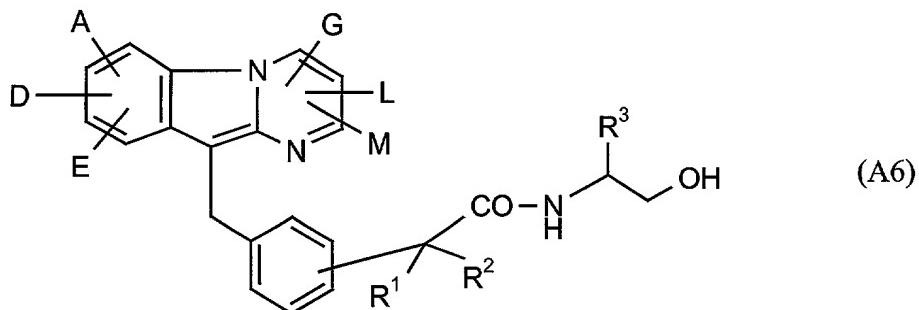
R⁴ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

R⁵ and R⁶ are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,
or denote straight-chain or branched acyl having up to 8 carbon atoms,
which is optionally substituted by a group of the formula -NR⁷R⁸,

in which

R⁷ and R⁸ are identical or different and
denote hydrogen or straight-chain or branched acyl having up to
8 carbon atoms,

or of the general formula (A6)



in which

A, D, E, G, L and M are identical or different and

represent hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

R¹ and R² are identical or different and

represent hydrogen, cycloalkyl having 3 to 8 carbon atoms or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms, or represent phenyl which is optionally substituted by halogen or trifluoromethyl, or

R¹ and R², together with the carbon atom, form a 4- to 8-membered cycloalkyl ring

and

R³ represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxycarbonyl each having up to 6 carbon atoms or by straight-chain

or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

and/or is optionally substituted by a group of the formula -OR⁴ or -NR⁵R⁶,

in which

R⁴ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

R⁵ and R⁶ are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,
or denote straight-chain or branched acyl having up to 8 carbon atoms,
which is optionally substituted by a group of the formula -NR⁷R⁸,

in which

R⁷ and R⁸ are identical or different and
denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

if appropriate in an isomeric form and their salts

and component B being at least one [with] HMG-CoA reductase inhibitor[s] [as component B for the production of medicaments for the prophylaxis and/or treatment of cardiovascular diseases].

- 43219802.2 1000
2. (Amended) [Use of a combination] The method according to Claim 1 [for the production of medicaments for the control or prophylaxis of] wherein said cardiovascular diseases [which] are associated with metabolic diseases or deficits.
 3. (Amended) [Use of a combination] The method according to Claim 2 for the control of arteriosclerosis, diseases of the coronary vessels of the heart, raised serum lipids, hypercholesterolaemia, hypertriglyceridaemia and mixed forms which are combined with raised VLDL or LDL and/or raised chylomicrons, and of syndrome X.
 4. (Amended) [Use of a combination] The method according to Claim 2 for the treatment of secondary hypercholesterolaemia and secondary hypertriglyceridaemia, which are optionally associated with apolipoprotein E polymorphism, obesity, chylomicronaemia and chylomicronaemia syndrome, renal insufficiency, chronic renal insufficiency, nephrotic syndrome, diabetes mellitus type II, and with hepatomas and plasmacytomas.
 5. (Amended) [Use of a combination] The method according to Claim 2, characterized in that [it contains, as] component A[,] is a compound of the general formula (A1).
 6. (Amended) [Use of a combination] The method according to Claim 2, characterized in that [it contains, as] component A[,] is a compound of Examples 1-119.
 7. (Amended) [Use of a combination] The method according to Claim 2, characterized in that [it contains, as] component A[,] is a compound of Examples 92-119.
 8. (Amended) [Use of a combination] The method according to Claim 2, characterized in that [it contains, as] component A[,] is a compound of Examples 48 or 80.

9. (Amended) [Medicament] A pharmaceutical composition comprising a combination of an MTP inhibitor as component A and an HMG-CoA reductase inhibitor as component B according to Claim 1 and, if appropriate, one or more further suitable components.
10. (Amended) [Medicament] A pharmaceutical composition according to Claim 9, characterized in that it contains, as component A, the active compound 2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide or 2-cyclopentyl-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide and, as component B, the active compound atorvastatin, cerivastatin, simvastatin, pravastatin, lovastatin, fluvastatin, itavastatin or ZD 4522.
11. (Amended) [Medicament] A pharmaceutical composition according to Claim 9, characterized in that it contains, as component A, the compound (2S)-2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-(1R)-hydroxy-1-phenyl-ethyl)-acetamide.
12. (Amended) [Process] A process for the production of [medicaments] a pharmaceutical composition according to Claim 9, characterized in that the components A and B are converted into a suitable administration form with excipients and vehicles and, if appropriate, with further components.

A combination of MTP inhibitors and HMG-CoA reductase inhibitors and the use thereof in medicaments

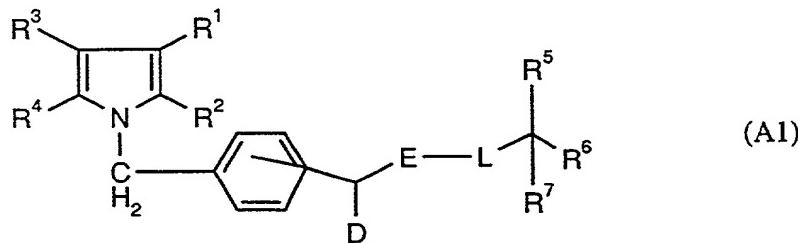
The invention relates to the use of a combination of at least one selected MTP inhibitor (component A) and one HMG-CoA reductase inhibitor (component B) for the control of cardiovascular diseases, to medicaments comprising this combination and to their production.

The compounds of component A have already been described as ApoB secretion inhibitors in the publications EP 705 831, EP 779 279, EP 779 276, EP 802 198 and EP 799 828. However, no reference to a combination with HMG-CoA reductase inhibitors is found.

HMG-CoA reductase inhibitors are a class of lipid-lowering agents which is well known to the person skilled in the art. In the context of this invention, statins preferred as HMG-CoA reductase inhibitors are described, for example, in EP 325 130 or US 5 177 080.

PCT WO 98/31366 and WO 98/03069 disclose combinations of MTP inhibitors with other cholesterol-lowering compounds. The MTP inhibitors actually mentioned there differ clearly, however, in their chemical structure from the selected MTP inhibitors which are claimed in the present invention.

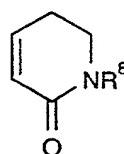
The subject of the present invention is the use of a combination of at least one MTP inhibitor as component A of the general formula (A1)



in which

R¹ and R², including the double bond connecting them, together form a phenyl or pyridyl ring or a ring of the formula

5



in which

10 R⁸ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R³ and R⁴, including the double bond connecting them, together form a phenyl ring or a 4- to 8-membered cycloalkene or oxocycloalkene radical,

15 all ring systems mentioned under R¹/R² and R³/R⁴ optionally being substituted up to 3 times, identically or differently, by halogen, trifluoromethyl, carboxyl, hydroxyl, by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

20

25 D represents hydrogen, cycloalkyl having 4 to 12 carbon atoms or straight-chain or branched alkyl having up to 12 carbon atoms,

E represents the -CO- or -CS- group,

L represents an oxygen or sulphur atom or a group of the formula -NR⁹,

in which

5 R⁹ denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or phenyl,

10 R⁵ denotes phenyl or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O,

15 the cyclic systems optionally being substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxy carbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms, and/or the cyclic systems optionally being substituted by a group of the formula -OR¹⁰ or -NR¹¹R¹²,

20 in which

25 R¹⁰ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

R¹¹ and R¹² are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms

or straight-chain or branched acyl having up to 8 carbon atoms, which is optionally substituted by a group of the formula -NR¹³R¹⁴,

30 in which

R¹³ and R¹⁴ are identical or different and denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

5 R⁶ represents hydrogen, carboxyl or straight-chain or branched alkoxy carbonyl having up to 5 carbon atoms,

10 or represents straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or by a group of the formula -O-CO-R¹⁵,

in which

15 R¹⁵ denotes phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl or by straight-chain or branched alkyl having up to 5 carbon atoms,

20 or denotes straight-chain or branched alkyl or alkenyl each having up to 22 carbon atoms, each of which is optionally substituted by a group of the formula -OR¹⁶,

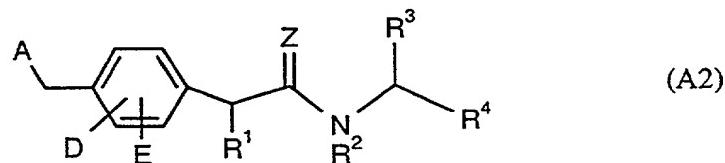
in which

25 R¹⁶ denotes hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 6 carbon atoms,

R⁷ represents hydrogen or

30 R⁶ and R⁷ together represent the group of the formula =O,

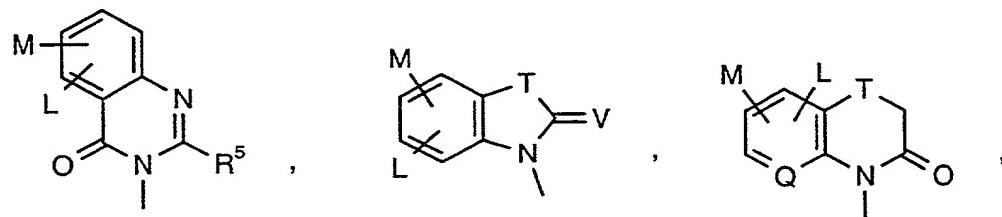
or of the general formula (A2)



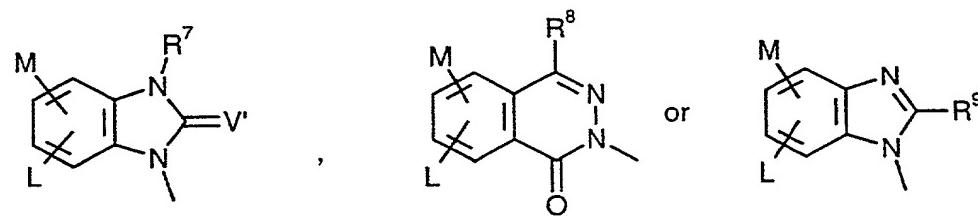
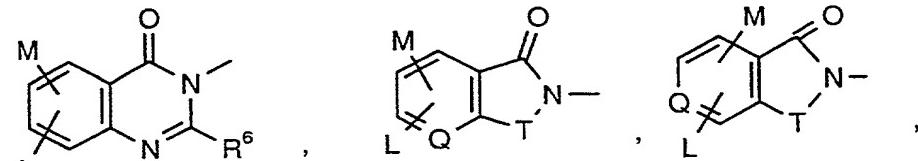
in which

5

A represents a radical of the formula



10



in which

15

L and M are identical or different and

denote hydrogen, halogen, trifluoromethyl, carboxyl, cycloalkyl having 3 to 6 carbon atoms, hydroxyl, phenyl or straight-chain or branched alkyl, alkoxy carbonyl or alkoxy each having up to 6 carbon

atoms,

Q denotes a nitrogen atom or the -CH- group,

5 T denotes a group of the formula -SO₂ or -CO or an oxygen or sulphur atom,

V denotes an oxygen or sulphur atom,

10 R⁵, R⁶, R⁷ and R⁸ are identical or different and denote hydrogen, or straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, each of which is optionally substituted by halogen or by straight-chain or branched alkyl having up to 6 carbon atoms,

15 R⁹ denotes trifluoromethyl, benzyl or a 5- to 7-membered, optionally benzo-fused heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, which is optionally substituted up to 3 times, identically or differently, by halogen, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms, or
20 denotes a group of the formula -S(O)_a-R¹⁰,

in which

25 a denotes a number 0, 1 or 2,

30 R¹⁰ denotes straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by straight-chain or branched acyl having up to 6 carbon atoms or by aryl or aroyl each having up to 10 carbon atoms, which

for their part can be substituted up to 2 times, identically or differently, by halogen, trifluoromethyl or by straight-chain or branched acyl having up to 5 carbon atoms, or

5

denotes aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, hydroxyl, trifluoromethyl or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms,

D and E are identical or different and

10

represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

Z represents an oxygen or sulphur atom,

15

R¹ represents cycloalkyl having 3 to 10 carbon atoms or straight-chain or branched alkyl having 1 to 10 carbon atoms, or represents phenyl which is optionally substituted up to 2 times, identically or differently, by halogen, nitro, cyano, hydroxyl, straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

20

R² represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

25

R³ represents hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or represents cycloalkyl having 3 to 7 carbon atoms, or represents phenyl or a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, each of which is optionally substituted up to 3 times, identically or differently, by halogen, nitro, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy

30

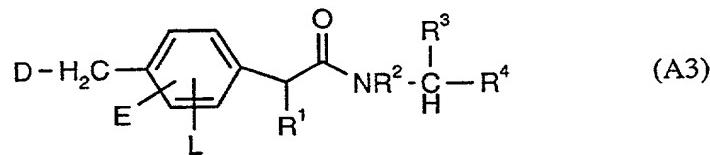
having up to 6 carbon atoms,

R⁴ represents hydrogen or a group of the formula -CH₂-OH or CH₂O-CO-R¹¹,

5 in which

R¹¹ denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms or phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl, cyano or straight-chain 10 or branched alkyl or alkoxy each having up to 4 carbon atoms,

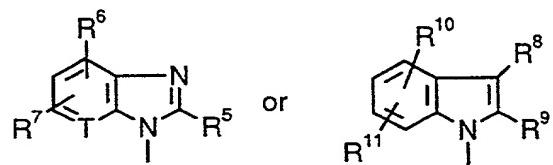
or of the general formula (A3)



15

in which

D represents a radical of the formula



20

in which

T denotes a nitrogen atom or the -CH- group,

25

R⁶, R⁷, R¹⁰ and R¹¹ are identical or different and

denote hydrogen, trifluoromethyl, halogen or straight-chain or branched alkyl
or alkoxy each having up to 6 carbon atoms,

R⁵, R⁸ and R⁹ are identical or different and

5 denote hydrogen, cycloalkyl having 3 to 6 carbon atoms, phenyl,
straight-chain or branched alkoxy carbonyl having up to 6 carbon
atoms or straight-chain or branched alkyl having up to 6 carbon atoms,
which is optionally substituted by halogen,

10 or, if T represents a nitrogen atom, R⁵ can also denote benzyl,

E and L are identical or different and

15 represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or
straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each
having up to 6 carbon atoms,

R¹ represents cycloalkyl having 3 to 10 carbon atoms or
straight-chain or branched alkyl having 1 to 10 carbon atoms, or

20 represents phenyl which is optionally substituted up to 2 times, identically or
differently, by halogen, cyano, hydroxyl, straight-chain or branched alkyl or
alkoxy each having up to 4 carbon atoms,

R² represents hydrogen or straight-chain or branched alkyl having up to 3 carbon
25 atoms,

R³ represents hydrogen or straight-chain or branched alkyl having up to 5 carbon
atoms, or
represents cycloalkyl having 3 to 7 carbon atoms, or
30 represents phenyl or a 5- to 7-membered aromatic heterocycle having up to
3 heteroatoms from the group consisting of S, N and/or O, each of which is

- 10 -

optionally substituted up to 3 times, identically or differently, by halogen, nitro, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having up to 6 carbon atoms,

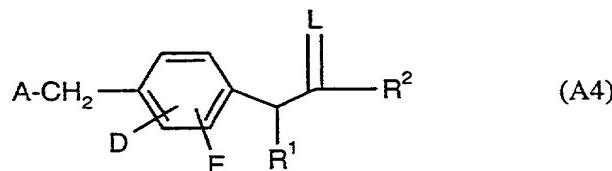
5 R⁴ represents hydrogen or a group of the formula -CH₂-OH or CH₂O-CO-R¹²,

in which

10 R¹² denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms or phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl, cyano or straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

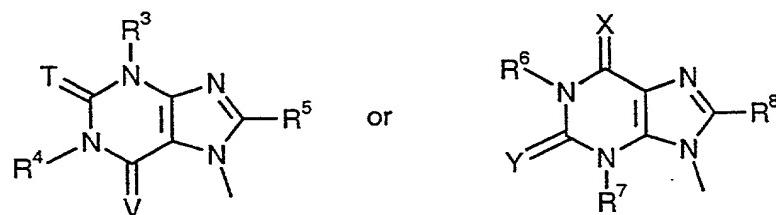
or of the general formula (A4)

15



in which

20 A represents a radical of the formula



in which

- R³, R⁴, R⁶ and R⁷ are identical or different and
denote hydrogen, cycloalkyl having 3 to 7 carbon atoms or aryl having
6 to 10 carbon atoms,
or denote straight-chain or branched alkyl or alkenyl each having up to
8 carbon atoms, each of which is optionally substituted by halogen,
hydroxyl or aryl having 6 to 10 carbon atoms,
- T, V, X and Y are identical or different and denote an oxygen or
sulphur atom,
- R⁵ and R⁸ are identical or different and
denote hydrogen, halogen, cycloalkyl having 3 to 8 carbon
atoms or straight-chain or branched alkyl or alkenyl each
having up to 8 carbon atoms, each of which is optionally
substituted by cycloalkyl having 3 to 8 carbon atoms, or by a 5-
to 6-membered, aromatic, optionally benzo-fused heterocycle
having up to 3 heteroatoms from the group consisting of S, N
and/or O, or by aryl having 6 to 10 carbon atoms, where the
cyclic systems for their part can be substituted up to 3 times,
identically or differently, by a 5- to 6-membered aromatic
heterocycle having up to 3 heteroatoms from the group
consisting of S, N and/or O, or by phenyl, benzyl, halogen,
hydroxyl, carboxyl or by straight-chain or branched alkyl,
alkoxy or alkoxy carbonyl each having up to 6 carbon atoms, or
denote aryl having 6 to 10 carbon atoms or a 5- to 7-membered
aromatic, optionally benzo-fused heterocycle having up to 3
heteroatoms from the group consisting of S, N and/or O, each
of which is optionally substituted up to 3 times, identically or
differently, by halogen, phenyl, trifluoromethyl, hydroxyl,
carboxyl or by straight-chain or branched alkyl, alkoxy or
alkoxy carbonyl each having up to 6 carbon atoms or by a group

- 12 -

of the formula -(CO)_a-NR⁹R¹⁰,

in which

5 a denotes a number 0 or 1,

R⁹ and R¹⁰ are identical or different and

denote hydrogen, phenyl or straight-chain or branched
alkyl or acyl each having up to 5 carbon atoms,

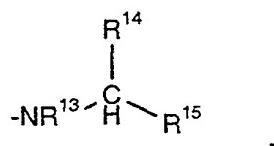
10 D and E are identical or different and
represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-
chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 6 carbon
atoms,

15 R¹ represents hydrogen or cycloalkyl having 3 to 8 carbon atoms, or
represents straight-chain or branched alkyl or alkenyl each having up to
8 carbon atoms, each of which is optionally substituted by cycloalkyl having 3
to 6 carbon atoms, phenyl or by a 5- to 6-membered aromatic heterocycle
having up to 3 heteroatoms from the group consisting of S, N and/or O, or
represents phenyl or a 5- to 6-membered aromatic heterocycle having up to
3 heteroatoms from the group consisting of S, N and/or O, the ring systems
optionally being substituted up to 3 times, identically or differently, by
halogen, phenyl, trifluoromethyl or straight-chain or branched alkyl or alkoxy
each having up to 5 carbon atoms, hydroxyl or by a group of the formula
20 -NR¹¹R¹²,

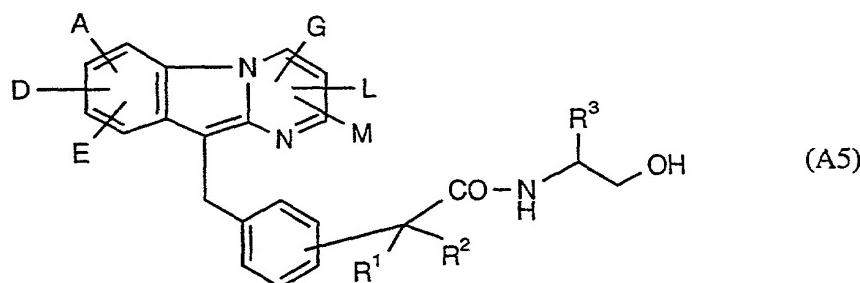
in which

25 R¹¹ and R¹² have the meaning of R⁹ and R¹⁰ indicated above and are
identical to or different from this,

- L represents an oxygen or sulphur atom,
- R² represents mercapto, hydroxyl, straight-chain or branched alkoxy having up to
5 carbon atoms or the group of the formula



- in which
- R¹³ denotes hydrogen or straight-chain or branched alkyl having up to
10 4 carbon atoms,
- R¹⁴ denotes hydrogen, phenyl or a 5- to 6-membered aromatic heterocycle
15 having up to 3 heteroatoms from the group consisting of S, N and/or
O,
- R¹⁵ denotes hydrogen or straight-chain or branched alkyl having up to
20 8 carbon atoms, which is optionally substituted by hydroxyl,
or of the general formula (A5)



in which

A, D, E, G, L and M are identical or different and

5 represent hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

10 R¹ and R² are identical or different and

represent hydrogen, cycloalkyl having 3 to 8 carbon atoms or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms or

15 represent phenyl which is optionally substituted by halogen or trifluoromethyl, or

R¹ and R², together with the carbon atom, form a 4- to 8-membered cycloalkyl ring

and

20

R³ represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxycarbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

25

and/or is optionally substituted by a group of the formula -OR⁴ or -NR⁵R⁶,

in which

30

R⁴ denotes hydrogen or straight-chain or branched alkyl or alkenyl each

having up to 6 carbon atoms,

R⁵ and R⁶ are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

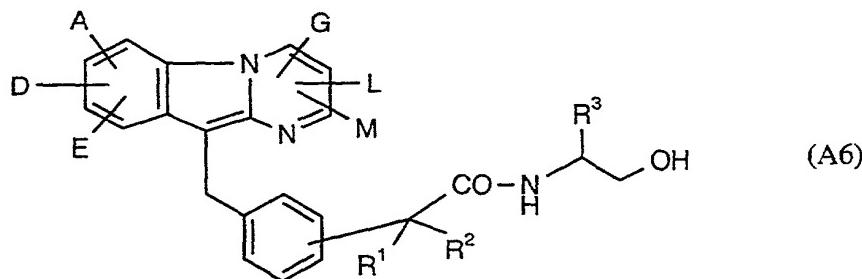
5 or denote straight-chain or branched acyl having up to 8 carbon atoms, which is optionally substituted by a group of the formula -NR⁷R⁸,

in which

10 R⁷ and R⁸ are identical or different and denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

or of the general formula (A6)

15



in which

20

A, D, E, G, L and M are identical or different and

represent hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

25

R¹ and R² are identical or different and

represent hydrogen, cycloalkyl having 3 to 8 carbon atoms or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms, or
5 represent phenyl which is optionally substituted by halogen or trifluoromethyl, or

R¹ and R², together with the carbon atom, form a 4- to 8-membered cycloalkyl ring

and

10

R³ represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxy carbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,
15 and/or is optionally substituted by a group of the formula -OR⁴ or -NR⁵R⁶,

in which

20

R⁴ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

25

R⁵ and R⁶ are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, or denote straight-chain or branched acyl having up to 8 carbon atoms, which is optionally substituted by a group of the formula -NR⁷R⁸,

in which

30

R⁷ and R⁸ are identical or different and

denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

if appropriate in an isomeric form and their salts

5

with HMG-CoA reductase inhibitors as component B in the prophylaxis and treatment of cardiovascular diseases, preferably those cardiovascular diseases which are associated with metabolic diseases or deficits, such as, for example, disorders of fat metabolism or of carbohydrate metabolism, such as, for example, diabetes.

10

The invention furthermore relates to pharmaceutical preparations comprising these combinations of the components A and B and to their preparation.

15

The compounds as in the general formula (A1) are of great interest as combination partners of component A, and likewise of particular importance are the compounds of the following Examples 1 to 119, in particular the compounds of Examples 92 to 119, very particularly the compounds of Examples 48 and 80, (2S)-2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-(1R)-hydroxy-1-phenyl-ethyl)-acetamide (Example 48) and (2S)-2-cyclopentyl-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-(1R)-hydroxy-1-phenyl-ethyl)-acetamide (Example 80).

20

25

30

In the context of the present invention, the use of the physiologically acceptable salts of the abovementioned MTP inhibitors is also claimed. Physiologically acceptable salts of the compounds according to the invention are, for example, salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred salts are, for example, those with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

SEARCHED
INDEXED
MAILED
FILED
JULY 2000
U.S. PATENT AND TRADEMARK OFFICE

Physiologically acceptable salts of the abovementioned MTP inhibitors can also be metal or ammonium salts of the compounds according to the invention which have a free carboxyl group. Those particularly preferred are, for example, sodium potassium, 5 magnesium or calcium salts, and ammonium salts which are derived from ammonia, or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine, ethylenediamine or 2-phenylethylamine.

10 The MTP inhibitors and HMG-CoA reductase inhibitors according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the enantiomers and diastereomers or their respective mixtures. These mixtures of the enantiomers and diastereomers can be separated into 15 the stereoisomerically uniform constituents in a manner known per se.

The combination of the selected MTP inhibitors as in the general formulae (A1)-(A6) as component A and HMG-CoA reductase inhibitors as component (B) is new.

20 It has now been found that the combinations according to the invention have unexpected valuable pharmacological properties, in particular they are suitable for the prophylaxis and treatment of diseases of the cardiovascular system which are associated with metabolic disorders.

25 In the context of the invention, HMG-CoA reductase inhibitors in general represent all substance classes mentioned under this term in the prior art. The abbreviation "HMG-CoA" here represents "3-hydroxy-3-methylglutaryl-coenzyme A". Under this term, statins are preferred, such as are described, for example in EP 247 633, US 5 006 530, EP 33 538, US 4346 227, EP 22 478 or EP 114 027.

30 The following may preferably be mentioned:

- atorvastatin (commercially obtainable under the name Lipitor[®] from Parke-Davis);
- cerivastatin (commercially obtainable under the name Lipobay[®] or Baycol[®] from Bayer);
- fluvastatin (commercially obtainable under the name Lescol[®] from Novartis);
- lovastatin (commercially available under the name Mevacor[®] from Merck);
- pravastatin (commercially obtainable under the name Lipostat[®] from Bristol-Myers Squibb);
- simvastatin (commercially obtainable under the name Zocor[®] from Merck);
- itavastatin (also called "Nisvastatin"; NK-104; systematic name: [S-[R*,S*-(E)]]-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid);
- dalvastatin;
- mevastatin;
- dihydrocompactin;
- compactin; and
- (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidin-5-yl)-3,5-dihydroxy-6(E)-heptenoic acid.

20

Statins are customarily employed as lactones (cf. e.g. lovastatin), esters or as carboxylic acids or as salts of the carboxylic acid (cf. e.g. cerivastatin sodium).

25

According to the invention, the statins can be employed in all suitable forms, i.e. in the form of the respective salts, hydrates, alcoholates, esters, lactones and tautomers.

30

Very particularly preferred among the statins are atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, itavastatin, simvastatin and (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidin-5-yl)-3,5-dihydroxy-6(E)-heptenoic acid and their respective salts, hydrates, alcoholates, esters, lactones and tautomers.

Very particularly preferred among these, in turn, are atorvastatin and in particular cerivastatin, and their respective salts, hydrates, alcoholates, esters, lactones and tautomers.

5

For further details of the abovementioned statins, reference is made to the treatments in *Drugs of the Future* 1994, 19(6), pages 537-541, and 1995, 20(6), page 611, and 1996, 21(6), page 642, their respective contents being fully included by way of reference.

10

With reference to the HMG-CoA reductase inhibitors, the term "salt" within the meaning of the present invention in each case means physiologically acceptable salts of the compounds concerned: these can be, for example, salts with mineral acids, carboxylic acids or sulphonic acids, in particular with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid or alternatively mixed salts thereof. However, it can also mean salts with customary bases, such as, for example, alkali metal salts (e.g. sodium or potassium salts), alkaline earth metal salts (e.g. calcium or magnesium salts) or ammonium salts, derived from ammonia or organic amines such as, for example, diethylamine, triethylamine, ethyldiisopropylamine, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine, 1-ephenamine or methyl-piperidine, and mixed salts thereof.

15

Examples of statin salts which can be used according to the invention are fluindostatin (the monosodium salt of fluvastatin); the monopotassium salt and the calcium salt of itavastatin; and the calcium salt of (+)-(3R,5S)-bis(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methane-sulphonylamino)-pyrimidin-5-yl)-3,5-dihydroxy-6(E)-heptenoic acid ("ZD 4522" or "S 4522" from Shionogi and AstraZeneca). Further examples of statin salts which can be used according to the

invention are the monosodium and the monopotassium salts and the calcium salts of cerivastatin, of atorvastatin and of pravastatin. The monosodium salt of cerivastatin ("cerivastatin sodium") is very particularly preferably employed.

5 Further preferred HMG-CoA reductase inhibitors are described in EP-A-0 325 130 and in EP-A-0-491 226, both in the name of Bayer AG, whose contents are included herewith by way of reference. The subject of EP-A-0 325 130 is substituted pyridines, and EP-A-0-491 226 describes substituted pyridylhydroxyheptenoic acid derivatives and their salts, among them in particular cerivastatin, which is
10 particularly preferred according to the invention (*Claim 6 EP-A-0 491 226*).

Likewise preferred according to the invention are the statins mentioned in WO-A-99/11263, whose disclosure is included by way of reference.

15 Equally preferred according to the invention are the HMG-CoA reductase inhibitors which are mentioned in the publication *Bioorganic & Medicinal Chemistry*, Vol. 5, No. 2, pages 437-444 (1997) whose disclosure is hereby fully included by way of reference.

20 A further review on HMG-CoA reductase inhibitors is contained in *Pharmazie in unserer Zeit*, 28th year, No. 3, pages 147-152 (1999).

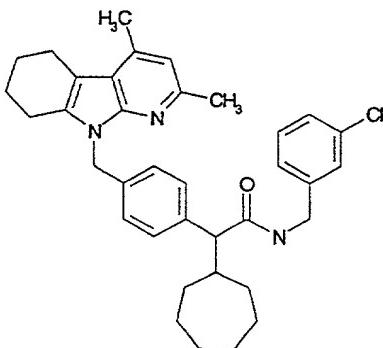
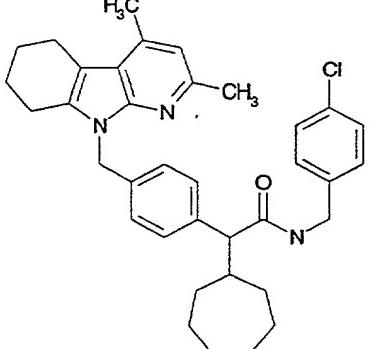
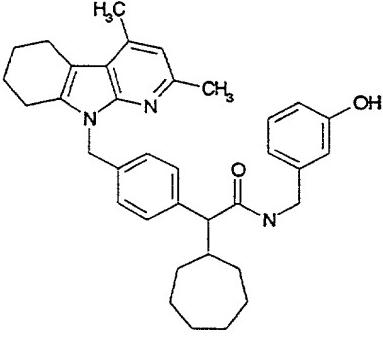
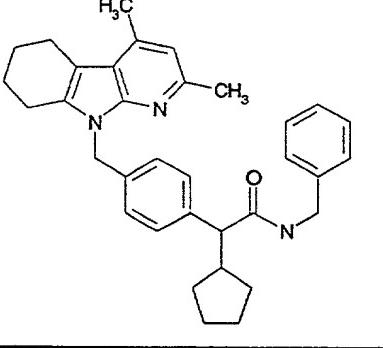
Preferred MTP inhibitors are the compounds shown in the following table:

P01/2009/2009/0001

Ex. No.	Structure	Name
1		2-Cyclopentyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
2		2-[4-(2-Butyl-benzoimidazol-1-ylmethyl)-phenyl]-2-cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
3		N-Benzyl-2-cycloheptyl-2-[4-(2-phenyl-benzoimidazol-1-ylmethyl)-phenyl]-acetamide
4		2-Cyclopentyl-2-[4-(1,3-dimethyl-2,6-dioxo-8-phenyl-1,2,3,6-tetrahydro-purin-7-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
5		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide

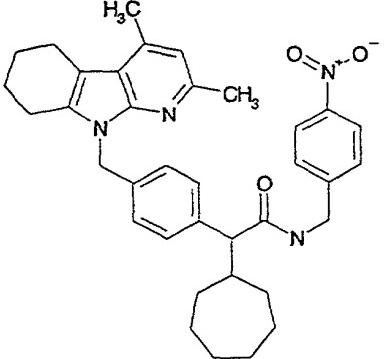
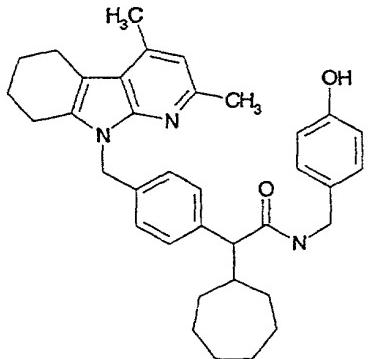
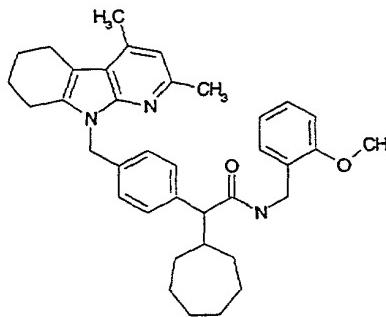
Ex. No.	Structure	Name
6		N-Benzyl-2-cycloheptyl-2-[4-(5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
7		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(4-methyl-2-propyl-benzoimidazol-1-ylmethyl)-phenyl]-acetamide
8		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
9		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-phenyl-benzoimidazol-1-ylmethyl)-phenyl]-acetamide

Ex. No.	Structure	Name
10		N-Benzyl-2-cycloheptyl-2-[4-(4-methyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
11		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-(4-indol-1-ylmethyl-phenyl)-acetamide
12		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-methyl-indol-1-ylmethyl)-phenyl]-acetamide
13		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(3-methyl-indol-1-ylmethyl)-phenyl]-acetamide
14		N-(2-Chloro-benzyl)-2-cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide

Ex. No.	Structure	Name
15		N-(3-Chloro-benzyl)-2-cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
16		N-(4-Chloro-benzyl)-2-cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
17		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(3-hydroxy-benzyl)-acetamide
18		N-Benzyl-2-cyclopentyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide

Ex. No.	Structure	Name
19		N-Benzyl-2-cycloheptyl-2-[4-(2-methyl-4-trifluoromethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
20		N-Benzyl-2-cycloheptyl-2-[4-(2,4-dimethyl-6,7,8,9-tetrahydro-5H-1,10-diaza-benzo[a]azulen-10-ylmethyl)-phenyl]-acetamide
21		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-methyl-benzimidazol-1-ylmethyl)-phenyl]-acetamide
22		2-(4-Benzimidazol-1-ylmethyl-phenyl)-2-cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-acetamide

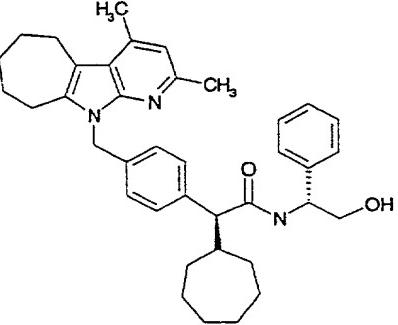
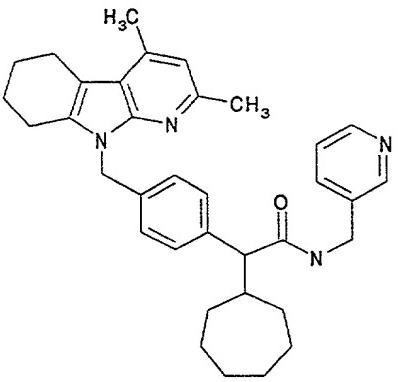
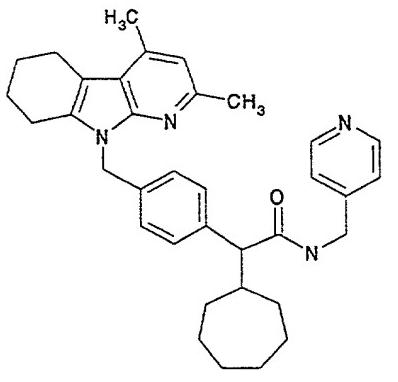
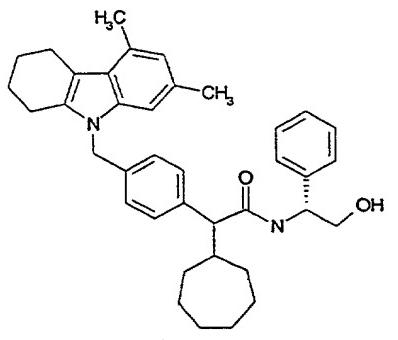
Ex. No.	Structure	Name
23		N-Benzyl-2-cycloheptyl-2-[4-(2-thiazol-4-ylbenzimidazol-1-ylmethyl)-phenyl]-acetamide
24		N-Benzyl-2-cycloheptyl-2-[4-(2-pyridin-2-ylbenzimidazol-1-ylmethyl)-phenyl]-acetamide
25		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydropyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-nitrobenzyl)-acetamide
26		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydropyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(3-nitrobenzyl)-acetamide

Ex. No.	Structure	Name
27		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(4-nitrobenzyl)-acetamide
28		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(4-hydroxybenzyl)-acetamide
29		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-methoxybenzyl)-acetamide

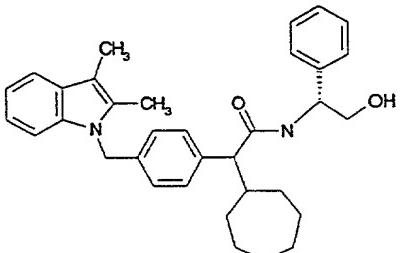
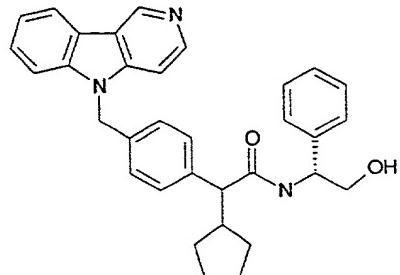
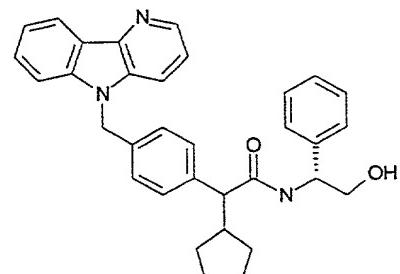
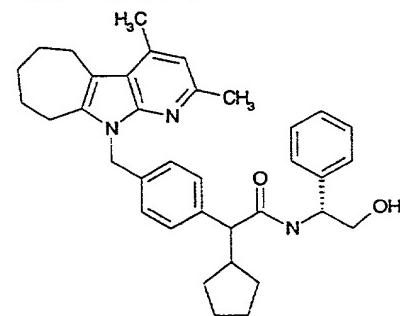
Ex. No.	Structure	Name
30	<p>Chemical structure 30: 2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(4-methoxy-benzyl)-acetamide</p>	
31	<p>Chemical structure 31: 4-{(2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetylamino}-methyl)-benzoic acid methyl ester</p>	
32	<p>Chemical structure 32: 2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(3-methylbenzyl)-acetamide</p>	
33	<p>Chemical structure 33: N-Benzyl-2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide</p>	

Ex. No.	Structure	Name
34		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-thioxo-2,3-dihydro-benzoimidazol-1-ylmethyl)-phenyl]-acetamide
35		N-Benzyl-2-cycloheptyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
36		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-methyl-4-trifluoromethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
37		N-Benzyl-2-cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide

Ex. No.	Structure	Name
38		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(4-hydroxymethyl-benzyl)-acetamide
39		2-Cycloheptyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
40		2-Cycloheptyl-2-[4-(4,6-dimethyl-2,3-dihydro-1H-7,8-diaza-cyclopenta[a]inden-8-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
41		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(4-methyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide

Ex. No.	Structure	Name
42		2-Cycloheptyl-2-[4-(2,4-dimethyl-6,7,8,9-tetrahydro-5H-1,10-diaza-benzo[a]azulen-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
43		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-pyridin-3-ylmethyl-acetamide
44		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-pyridin-4-ylmethyl-acetamide
45		2-Cycloheptyl-2-[4-(5,7-dimethyl-1,2,3,4-tetrahydro-carbazol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide

Ex. No.	Structure	Name
46		2-Cycloheptyl-2-[4-(5,7-dimethyl-1,2,3,4-tetrahydrocarbazol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenylethyl)-acetamide
47		2-Cycloheptyl-N-(2-hydroxy-1-phenylethyl)-2-[4-(1,1,3-trioxo-1,3-dihydro-1,6-benzo[d]isothiazol-2-ylmethyl)-phenyl]-acetamide
48		(2S)-2-Cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-(1R)-hydroxy-1-phenylethyl)-acetamide
49		2-Cycloheptyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydropyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(3-hydroxymethyl-benzyl)-acetamide
50		2-Cycloheptyl-N-(2-hydroxy-1-phenylethyl)-2-[4-(2-phenyl-benzoimidazol-1-ylmethyl)-phenyl]-acetamide

Ex. No.	Structure	Name
51		2-Cycloheptyl-2-[4-(2,3-dimethyl-indol-1-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
52		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-(4-pyrido[4,3-b]indol-5-ylmethyl-phenyl)-acetamide
53		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-(4-pyrido[3,2-b]indol-5-ylmethyl-phenyl)-acetamide
54		2-Cyclopentyl-2-[4-(2,4-dimethyl-6,7,8,9-tetrahydro-5H-1,10-diaza-benzo[a]azulen-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide

Ex. No.	Structure	Name
55		2-Cyclopentyl-2-[4-(5,7-dimethyl-1,2,3,4-tetrahydrocarbazol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenylethyl)-acetamide
56		2-Cycloheptyl-N-(2-hydroxy-1-phenylethyl)-2-[4-(2-thiazol-4-yl-benzoimidazol-1-ylmethyl)-phenyl]-acetamide
57		2-Cycloheptyl-2-[4-(5,6-dimethyl-benzoimidazol-1-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenylethyl)-acetamide
58		2-Cycloheptyl-N-(2-hydroxy-1-phenylethyl)-2-[4-(2-pyridin-2-yl-benzoimidazol-1-ylmethyl)-phenyl]-acetamide

Ex. No.	Structure	Name
59		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-methylsulfanyl-benzimidazol-1-ylmethyl)-phenyl]-acetamide
60		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-thiazol-4-yl-benzimidazol-1-ylmethyl)-phenyl]-acetamide
61		2-[4-(8-Bromo-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl)-phenyl]-2-cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
62		2-[4-(8-Benzyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl)-phenyl]-2-cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-acetamide

1000190007 * 122104

Ex. No.	Structure	Name
63		2-Cyclohexyl-2-[4-(2,4-dimethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
64		2-[4-(2,4-Dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-4-methyl-pentanoic acid (2-hydroxy-1-phenyl-ethyl)-amide
65		2-Cycloheptyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-methyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
66		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-methyl-4-trifluoromethyl-5,6,7,8-tetrahydro-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide

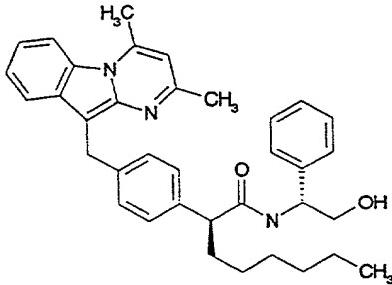
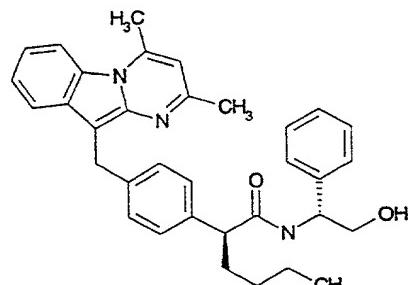
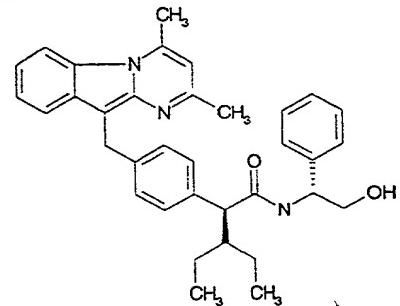
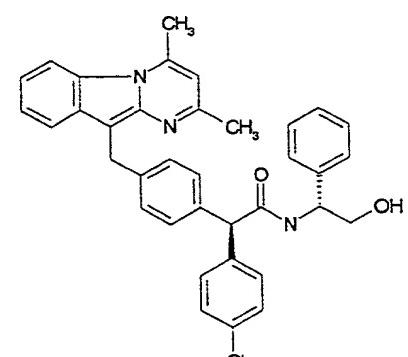
Ex. No.	Structure	Name
67		2-Cyclohexyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
68		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-methyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
69		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(4-methyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
70		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-methyl-1-oxo-1,2,3,4-tetrahydro-β-carolin-9-ylmethyl)-phenyl]-acetamide

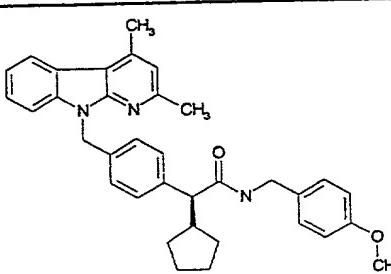
Ex. No.	Structure	Name
71		2-[4-(2,4-Dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-3-methylbutyramide
72		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(2-methyl-4-trifluoromethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide
73		2-Cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-thioacetamide
74		2-Cyclopentyl-2-{4-[8-(4-fluoro-benzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl]-phenyl}-N-(2-hydroxy-1-phenyl-ethyl)-acetamide

Ex. No.	Structure	Name
75		2-[4-[8-(2-Chloro-benzyl)-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl]-phenyl]-2-cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
76		2-Cyclopentyl-2-[4-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1,3,9-triaza-fluoren-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
77		2-[4-(8-Cyclohexylmethyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-purin-7-ylmethyl)-phenyl]-2-cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
78		2-Cyclopentyl-2-[4-(1,3-dimethyl-2,6-dioxo-8-m-tolyl-1,2,3,6-tetrahydro-purin-7-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide

Ex. No.	Structure	Name
79		2-Cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-[2-hydroxy-1-(3-hydroxy-phenyl)-ethyl]-acetamide
80		(2S)-2-Cyclopentyl-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-(1R)-hydroxy-1-phenyl-ethyl)-acetamide
81		2-Cyclopentyl-2-[4-(2,4-dimethyl-1,3-dioxo-1,2,3,4,5,6,7,8-octahydro-2,4,9-triaza-fluoren-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
82		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(3-methyl-pyrido[3,2-b]indol-5-ylmethyl)-phenyl]-acetamide

Ex. No.	Structure	Name
83		1-[4-(2,4-Dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-cyclohexanecarboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide
84		2-Cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-thiophen-2-yl-ethyl)-acetamide
85		1-[4-(2,4-Dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-cyclopentanecarboxylic acid (2-hydroxy-1-phenyl-ethyl)-amide
86		2-[4-(2,4-Dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-heptanoic acid (2-hydroxy-1-phenyl-ethyl)-amide

Ex. No.	Structure	Name
87		2-[4-(2,4-Dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-octanoic acid (2-hydroxy-1-phenyl-ethyl)-amide
88		2-[4-(2,4-Dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-hexanoic acid (2-hydroxy-1-phenyl-ethyl)-amide
89		2-[4-(2,4-Dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-3-ethyl-pentanoic acid (2-hydroxy-1-phenyl-ethyl)-amide
90		2-(4-Chloro-phenyl)-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide

Ex. No.	Structure	Name
91		2-Cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(4-methoxy-benzyl)-acetamide

AUGUST 2006 EDITION

Particularly preferred MTP inhibitors are the compounds shown in the following table

Ex. No.	Structure	Name
92		2-Cyclopentyl-2-[4-(1,3-dimethyl-pyrido[4,3-b]indol-5-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
93		2-Cyclopentyl-2-[4-(2,3-dimethyl-1,4-dioxo-1,2,3,4-tetrahydro-2,3,9-triazafluoren-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
94		2-Cyclopentyl-2-[4-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydro-2,4,9-triazafluoren-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
95		2-[4-(2,4-Dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-5-methylhexanoic acid (2-hydroxy-1-phenyl-ethyl)-amide

Ex. No.	Structure	Name
96		2-[4-(2,4-Dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-4-methylpentanoic acid (2-hydroxy-1-phenylethyl)-amide
97		2-Cycloheptyl-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenylethyl)-acetamide
98		2-Cyclohexyl-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenylethyl)-acetamide
99		2-Cyclopentyl-N-(2-hydroxy-1-phenylethyl)-2-[4-(2,3,4-trimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-acetamide
100		2-[4-(8-Chloro-2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-2-cyclopentyl-N-(2-hydroxy-1-phenylethyl)-acetamide

Ex. No.	Structure	Name
101		2-[4-(2,4-Dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-pentanoic acid (2-hydroxy-1-phenyl-ethyl)-amide
102		2-Cyclopentyl-2-[4-(3-ethyl-2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
103		2-Cyclooctyl-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
104		2-[4-(7-Chloro-2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-2-cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
105		N-(4-Chloro-benzyl)-2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-acetamide

100190037-122407

Ex. No.	Structure	Name
106		2-Cyclopentyl-2-[4-(4-ethyl-2,3-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
107		2-Cyclopentyl-2-[4-(2-ethyl-3,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
108		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(8-methoxy-2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-acetamide
109		3-Cyclopentyl-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-propionamide
110		2-Cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(7-methoxy-2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-acetamide

Ex. No.	Structure	Name
111		2-Cyclopentyl-2-[4-(4-ethyl-2-methyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
112		2-Cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(3-hydroxy-benzyl)-acetamide
113		N-Benzyl-2-cyclopentyl-2-[4-(2,4-dimethyl-1,3,9-triaza-fluoren-9-ylmethyl)-phenyl]-acetamide
114		2-Cyclopentyl-2-[4-(2,4-dimethyl-1,3,9-triaza-fluoren-9-ylmethyl)-phenyl]-N-(4-hydroxy-benzyl)-acetamide
115		2-Cyclopentyl-2-[4-(2,4-dimethyl-1,3,9-triaza-fluoren-9-ylmethyl)-phenyl]-N-pyridin-4-ylmethyl-acetamide

Ex. No.	Structure	Name
116		2-Cyclopentyl-2-[4-(2,4-dimethyl-1,3,9-triaza-fluoren-9-ylmethyl)-phenyl]-N-(4-methoxy-benzyl)-acetamide
117		4-(2-Cyclopentyl-2-[4-(2,4-dimethyl-1,3,9-triaza-fluoren-9-ylmethyl)-phenyl]-acetylamino)-methyl-benzoic acid methyl ester
118		2-Cyclopentyl-2-[4-(2,4-dimethyl-1,3,9-triaza-fluoren-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide
119		2-Cyclopentyl-2-[4-(2-ethyl-4-methyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide

- The combinations according to the invention exhibit a broad and versatile spectrum of action. They can be employed, for example, for the treatment and/or prophylaxis of arteriosclerosis, stroke, angina, diseases of the coronary vessels of the heart, in particular of the arterial coronary vessels, heart failure, primary and secondary myocardial infarct, pathological changes in the vessel wall, blood circulation disorders, disorders of the microcirculation, proliferation of smooth muscle cells, fat metabolic disorders with increased concentration of lipoproteins in the serum and possibly a shift in the proportions of lipoprotein, raised serum lipids, hyperlipoproteinaemia, hypercholesterolaemia, hypertriglyceridaemia, raising both of the serum cholesterol and the serum triglycerides combined with raised VLDL (very low density lipoprotein) and raising of the chylomicrons in the plasma, insulin resistance, IGT (impaired glucose tolerance), diabetes, non-insulin-dependent diabetes mellitus (= *type 2 diabetes*), hyperglycaemia, metabolic disorders such as disorders of the lipid metabolism, deficiency of acidic lipase, storage diseases, in particular fat storage diseases, phytosterolaemia, high blood pressure, osteoporosis, obesity, syndrome X, thrombosis, pancreatitis, constipation (obstipation), functional disorders of the brain, cerebrovascular insufficiency, cerebral blood circulation disorders, apoplexy, transitory ischaemic attacks (TIA) and fainting.
- Of particular interest is the treatment and prophylaxis of diseases which are influenced or caused by more than one risk factor, such as, for example, arteriosclerosis, disorders of the coronary vessels of the heart, in particular of the arterial coronary vessels, raised serum lipids, hypercholesterolaemia, hypertriglyceridaemia, raising both of serum cholesterol and of serum triglycerides combined with raised VLDL (very low density lipoprotein) or LDL (low density lipoprotein), and/or raising of the chylomicrons, e.g. chylomicronaemia, in the plasma and syndrome X.
- The combinations according to the invention are furthermore suitable for the treatment of secondary hypercholesterolaemia and secondary hypertriglyceridaemia

which are associated, for example, with apolipoprotein E polymorphism (e.g. apolipoprotein phenotype E 4/4 or E 3/4), obesity, chylomicronaemia and chylomicronaemia syndrome, renal insufficiency, chronic renal insufficiency, nephrotic syndrome, diabetes mellitus type II, and with hepatomas and
5 plasmacytomas.

The combinations according to the invention of the components A and B, in particular the special combination of (2S)-2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-(1R)-hydroxy-1-phenyl-ethyl)-

10 acetamide and cerivastatin, prove surprisingly advantageous in the treatment of coronary heart disorders, cardiac insufficiency, disorder of the brain function, apoplexy, blood circulation disorders and disorders of fat metabolism. An example which may be mentioned is dyslipidaemias, such as occur in diabetics but also in patients who do not suffer from diabetes. When using the combinations according to
15 the invention, a synergistic effect which is not to be expected, for example in the lowering of the LDL (low density lipoprotein) level, is observed in the action. The amounts of the components A and B employed can thus be decreased in comparison with monotherapy.

20 If appropriate, it may be expedient to supplement the combination according to the invention of MTP inhibitors and HMG-CoA reductase inhibitors by addition of one or more further components. An example which may be mentioned is vitamins, preferably all fat-soluble vitamins, in particular vitamins A and E. These vitamins or other components can be added individually or alternatively together. A further example of an additional component which may be mentioned is acetylsalicylic acid.
25

"Dyslipidaemia" is to be understood here as meaning either hypertriglyceridaemia or hypercholesterolaemia, but particularly mixed hyperlipidaemia, i.e. a disease state having a raised cholesterol level (LDL and total cholesterol) and raised triglyceride level. This can be associated with a reduction of the HDL (high density lipoprotein)
30 cholesterol in the plasma or a disturbed HDL-C/LDL-C ratio.

In particular, the combinations according to the invention are also suitable for the treatment of dyslipidaemias in diabetics or insulin resistance and IGT (impaired glucose tolerance).

5

On account of their action on the serum lipid level, the combinations according to the invention are furthermore particularly suitable for the prophylaxis and treatment of arteriosclerosis.

10

The combinations according to the invention are furthermore distinguished by a surprisingly good tolerability, although references to disadvantageous actions are to be found in the literature, such as, for example, warnings against the combination of statins with lipid-lowering agents.

15

The combinations according to the invention are preferably employed in human medicine, but they are also suitable for veterinary medicine, in particular for the treatment of mammals.

20

The combinations according to the invention can be administered parenterally or preferably orally.

25

The active compounds of components A and B can be converted in a known manner into the customary formulations, where these can be liquid or solid formulations. Examples are tablets, coated tablets, pills, capsules, granules, aerosols, syrups emulsions, suspensions, juices.

30

Since the combinations according to the invention are highly tolerable and active even in low doses, all sorts of formulation variants can be produced. Thus, on the one hand, there is the possibility of formulating the individual components separately. In this case, the two individual components A and B do not necessarily have to be taken at the same time, but on the contrary sequential taking can be advantageous for

DEUTSCHE PATENT- UND MARKENBÜRO
FÜR DRUGS & PHARMACEUTICALS

achieving optimal effects. In the case of a separate administration of this type, it is suggested to combine the formulations of the two individual components, for example tablets or capsules, at the same time next to one another in a suitable primary packaging.

5

Further formulation variants which are suitable for the combinations according to the invention are preferably also fixed combinations. "Fixed combination" is to be understood here as meaning those pharmaceutical forms in which the two components are present together in a fixed quantitative ratio. Such fixed combinations can be produced, for example, as peroral solutions, but they are preferably solid oral pharmaceutical preparations, e.g. capsules or tablets.

10

The combinations according to the invention are given up to 3× daily, those combinations being preferred which allow administration 1× daily.

15

The combinations according to the invention preferably contain 0.01 to 20 mg/kg, in particular 0.1 to 5 mg/kg, of active compound of component A, and 0.001 to 30 mg/kg, in particular 0.005 to 10 mg/kg, of active compound of component B, in each case relative to kg of body weight of the patient on oral administration.

20

25

If appropriate, it may be necessary to depart from the amounts mentioned, namely depending on the body weight or the type of administration route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus in some cases it may be adequate to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned has to be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these into a number of individual doses over the course of the day.

30

The active compounds of components A and B are particularly suitable for formulating in a fixed combination in the form of a solid peroral administration form.

It is generally known that the reliability of taking (compliance) in the case of patients is dependent to a decisive extent on the factors: number of administration forms per time of taking and size and weight of the (solid peroral) pharmaceutical form. The number of the different medicaments to be taken separately should therefore be as low as possible (advantage of a fixed combination), and the size and the weight of a solid peroral administration form should be as small as possible while retaining full therapeutic potency, in order to make taking as pleasant as possible for the patient. Fixed combinations can thus be produced in the form of solid peroral pharmaceutical formulations having minimal size and minimal weight. The fixed combinations according to the invention accordingly offer the highest possible patient compliance and thereby improve the safety and reliability of a therapy decisively.

The release of active compound can be controlled by combination of the two components A and B and modification of the composition or the functionality. For example, by delayed release of active compound (retardation) of one component, the abovementioned temporal uncoupling of the onset of action can be realized even in fixed combinations.

The solid peroral administration forms mentioned here are produced by the general standard procedures. Ingredients are those which are pharmaceutically accepted and physiologically acceptable, for example: as fillers cellulose derivatives (e.g. microcrystalline cellulose), sugars (e.g. lactose), sugar alcohols (e.g. mannitol, sorbitol), inorganic fillers (e.g. calcium phosphates), binding agents (e.g. polyvinylpyrrolidone, gelatin, starch and cellulose derivatives), and also all further excipients which are needed for the production of pharmaceutical formulations with the desired properties, e.g. lubricants (magnesium stearate), disintegrants (e.g. cross-linked polyvinylpyrrolidone, sodium carboxymethylcellulose), wetting agents (e.g. sodium laurylsulphate), retarding agents (e.g. cellulose derivatives, polyacrylic acid derivatives), stabilizers, aromas, colour pigments.

Liquid formulations are likewise prepared by a standard method using

pharmaceutically customary excipients and contain the active compound or the two active compounds in either dissolved or suspended form. Typical administration volumes of these pharmaceutical preparations are 1 to 10 ml. Examples of excipients in these liquid formulations are: solvents (e.g. water, alcohol, natural and synthetic oils, e.g. medium-chain triglycerides), solubilizers (e.g. glycerol, glycol derivatives), wetting agents, (e.g. polysorbate, sodium laurylsulphate), and further excipients which are needed for the production of pharmaceutical formulations with the desired properties, e.g. viscosity-increasing agents, pH correctants, sweeteners and flavourings, antioxidants, stabilizers, preservatives.

10

The main constituent of the shells of capsule formulations is, for example, gelatin or hydroxypropylmethylcellulose.

15

Pharmaceutical excipients which are familiar to the person skilled in the art are also described, for example, in the following handbook: "Handbook of Pharmaceutical Excipients", Wade, A. & Weller, P.J., American Pharmaceutical Association, Washington, 2nd Edition 1994.

Example

20

The changes in the serum triglycerides of dogs in % after 6 and 10 days' oral treatment with 0.03 mg of cerivastatin/kg or 4 mg/kg of body weight (BW) of the compound according to Example 48 or with the combination of the two active compounds in this dose were investigated. The results are summarized in Table 1.

25

Table 1

Group	Dog(s)	Day 6	Day 10
Control	5	-14	-3
Cerivastatin 0.03 mg/kg of BW	4	-10	-6
Ex. 48 4 mg/kg of BW	4	-15	-7
Cerivastatin 0.03 mg/kg + Ex. 48 4 mg/kg	5	-36	-31

The data were specifically determined as follows:

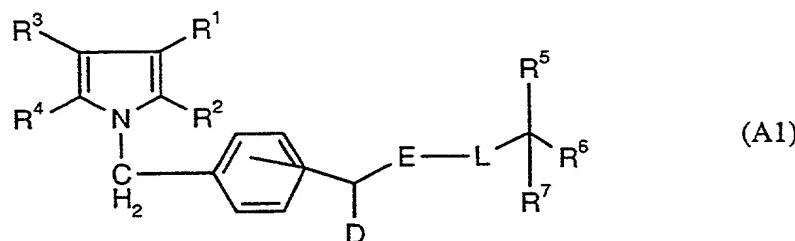
- 5 The serum triglyceride-lowering action of the substances was tested on dogs of both sexes (beagle, breeder: Marshall Farms, Inc. North Rose, NY, USA). The dogs (9 female and 9 male) were assigned to the groups randomly, care being taken that the sexes were assigned to the groups equally.
- 10 Control group: 3 male and 2 female dogs
 Cerivastatin group: 2 male and 2 female dogs
 Ex. 48 group: 2 male and 2 female dogs
 Combination group (cerivastatin + Ex. 48): 3 female and 2 male dogs
- 15 At the start of the experiment, the body weights of the dogs were 8.3 to 12.7 kg. For administration, the substances were mixed with canned food (Top Dog, Sniff, Soest, Germany) in an administration volume of 10 g/kg of BW.
- 20 1) The control animals (n=5) received the corresponding amount of canned food without substances
 2) Ex. 48 (n=4) was mixed with the canned food as a coprecipitate (20 mg/kg of BW) corresponding to a dose of active compound of 4 mg/kg of BW).

- 3) Cerivastatin (n=4) was administered in a dose of 0.03 mg/kg of BW. For this, cerivastatin was dissolved in an administration volume of 0.1 ml of water/kg of BW and the appropriate amount was mixed with the canned food.
- 5 4) In the combination (n=5), both substances corresponding to a dose of 0.03 mg of cerivastatin/kg of BW and 4 mg of Ex. 48/kg of BW were mixed into the canned food and administered to the animals.
- 10 The dogs received the substances once daily in the morning, then the animals received a dog maintenance diet (Sniff HD-H, Soest, Germany) ad libitum.
- 15 For triglyceride determination, blood was taken from the jugular vein of the animals. The blood samples were taken directly before the first substance administration around 09.00 (morning), on day 6 after the start of treatment 23 hours after substance administration and on day 10 after the start of treatment 23 hours after the last treatment. The blood was collected in heparinized LH monovettes and centrifuged. The triglycerides in the plasma were determined enzymatically using a commercially available test kit (Boehringer Mannheim, Germany) on an EPOS analyser (Eppendorf Gerätebau, Netheler und Hinz, Hamburg, Germany).
- 20 The individual differences in the plasma triglyceride concentrations after treatment to the corresponding preliminary values before the first substance administration were calculated, and these were averaged and indicated as the percentage change from the preliminary value.

Patent Claims

1. Use of a combination of at least one MTP inhibitor as component A of the general formula (A1)

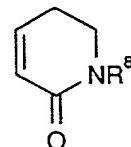
5



in which

R¹ and R², including the double bond connecting them, together form a phenyl or pyridyl ring or a ring of the formula

10



in which

15

R⁸ denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R³ and R⁴, including the double bond connecting them, together form a phenyl ring or a 4- to 8-membered cycloalkene or oxocycloalkene radical,

20

all ring systems mentioned under R¹/R² and R³/R⁴ optionally being substituted up to 3 times, identically or differently, by halogen, trifluoromethyl, carboxyl, hydroxyl, by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or by

straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

5 D represents hydrogen, cycloalkyl having 4 to 12 carbon atoms or straight-chain or branched alkyl having up to 12 carbon atoms,

E represents the -CO- or -CS- group,

10 L represents an oxygen or sulphur atom or a group of the formula -NR⁹,

in which

15 R⁹ denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or phenyl,

20 R⁵ denotes phenyl or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O,

25 the cyclic systems optionally being substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxy carbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

30 and/or the cyclic systems optionally being substituted by a group of the formula -OR¹⁰ or -NR¹¹R¹²,

in which

5 R¹⁰ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

10 R¹¹ and R¹² are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms or straight-chain or branched acyl having up to 8 carbon atoms, which is optionally substituted by a group of the formula -NR¹³R¹⁴,

in which

15 R¹³ and R¹⁴ are identical or different and denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

20 R⁶ represents hydrogen, carboxyl or straight-chain or branched alkoxy carbonyl having up to 5 carbon atoms, or represents straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or by a group of the formula -O-CO-R¹⁵,

25 in which

30 R¹⁵ denotes phenyl which is optionally substituted up to 3 times, identically or differently, by halogen; hydroxyl or by straight-chain or branched alkyl having up to 5 carbon atoms, or denotes straight-chain or branched alkyl or alkenyl each having up to 22 carbon atoms, each of which is optionally

substituted by a group of the formula -OR¹⁶,

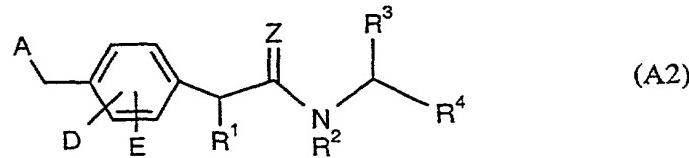
in which

5 R¹⁶ denotes hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 6 carbon atoms,

R⁷ represents hydrogen or

10 R⁶ and R⁷ together represent the group of the formula =O,

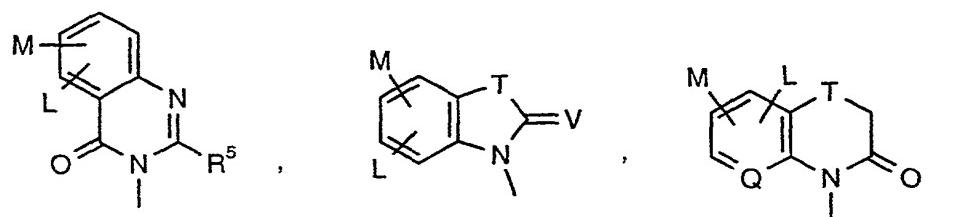
or of the general formula (A2)



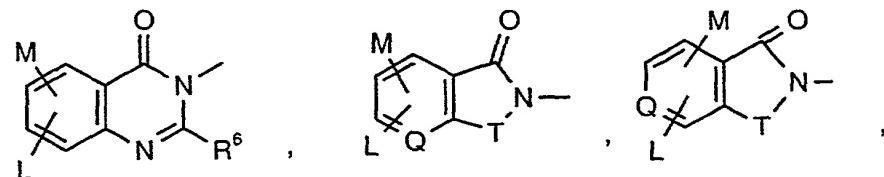
15

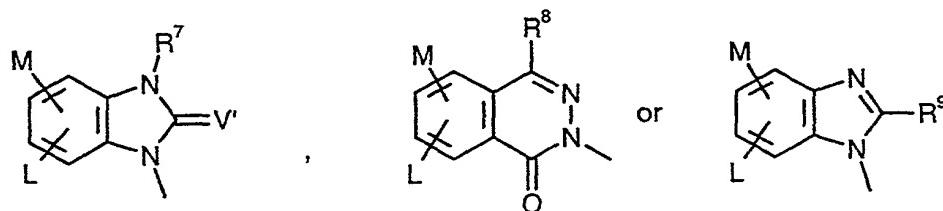
in which

A represents a radical of the formula



20





in which

5

L and M are identical or different and

denote hydrogen, halogen, trifluoromethyl, carboxyl, cycloalkyl having 3 to 6 carbon atoms, hydroxyl, phenyl or straight-chain or branched alkyl, alkoxy carbonyl or alkoxy each having up to 6 carbon atoms,

10

Q denotes a nitrogen atom or the -CH- group,

15

T denotes a group of the formula -SO₂ or -CO or an oxygen or sulphur atom,

V denotes an oxygen or sulphur atom,

20

R⁵, R⁶, R⁷ and R⁸ are identical or different and

denote hydrogen, or straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, each of which is optionally substituted by halogen or by straight-chain or branched alkyl having up to 6 carbon atoms,

25

R⁹ denotes trifluoromethyl, benzyl or a 5- to 7-membered, optionally benzo-fused heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, which is optionally substituted up to 3 times, identically or differently, by halogen,

phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms, or denotes a group of the formula $-S(O)_a-R^{10}$,

5 in which

a denotes a number 0, 1 or 2,

10 R^{10} denotes straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by straight-chain or branched acyl having up to 6 carbon atoms or by aryl or aroyl each having up to 10 carbon atoms, which for their part can be substituted up to 2 times, identically or differently, by halogen, trifluoromethyl or by straight-chain or branched acyl having up to 5 carbon atoms, or
15 denotes aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, hydroxyl, trifluoromethyl or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms,
20

D and E are identical or different and

25 represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

Z represents an oxygen or sulphur atom,

30 R^1 represents cycloalkyl having 3 to 10 carbon atoms or straight-chain or branched alkyl having 1 to 10 carbon atoms, or represents phenyl which is optionally substituted up to 2 times,

identically or differently, by halogen, nitro, cyano, hydroxyl, straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

5 R² represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

10 R³ represents hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or
 represents cycloalkyl having 3 to 7 carbon atoms, or
 represents phenyl or a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, each of which is optionally substituted up to 3 times, identically or differently, by halogen, nitro, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having up to 6 carbon atoms,

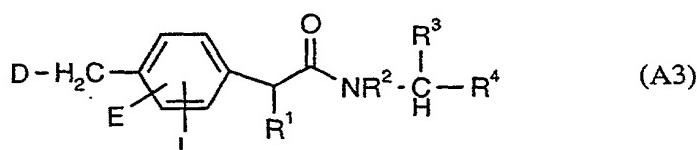
15 R⁴ represents hydrogen or a group of the formula -CH₂-OH or CH₂O-CO-R¹¹,

in which

20 R¹¹ denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms or phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl, cyano or straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

25

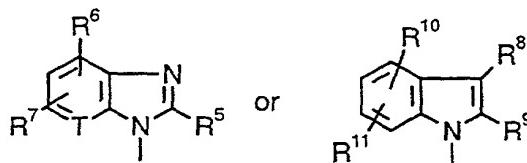
or of the general formula (A3)



in which

D represents a radical of the formula

5



in which

10

T denotes a nitrogen atom or the -CH- group,

R⁶, R⁷, R¹⁰ and R¹¹ are identical or different and

denote hydrogen, trifluoromethyl, halogen or straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms,

15

R⁵, R⁸ and R⁹ are identical or different and

denote hydrogen, cycloalkyl having 3 to 6 carbon atoms, phenyl, straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by halogen,

20

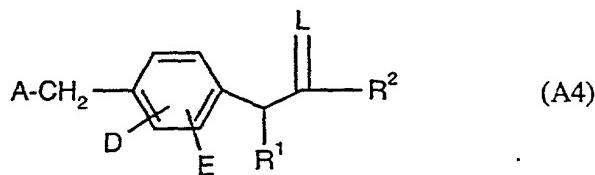
or, if T represents a nitrogen atom, R⁵ can also denote benzyl,

E and L are identical or different and

25

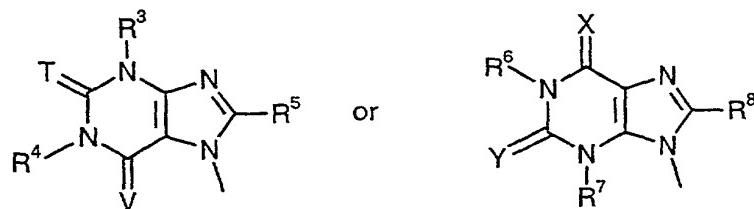
represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

- 5 R¹ represents cycloalkyl having 3 to 10 carbon atoms or straight-chain or branched alkyl having 1 to 10 carbon atoms, or represents phenyl which is optionally substituted up to 2 times, identically or differently, by halogen, cyano, hydroxyl, straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,
- 10 R² represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,
- 15 R³ represents hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, or represents cycloalkyl having 3 to 7 carbon atoms, or represents phenyl or a 5- to 7-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, each of which is optionally substituted up to 3 times, identically or differently, by halogen, nitro, phenyl, hydroxyl or by straight-chain or branched alkyl or alkoxy having up to 6 carbon atoms,
- 20 R⁴ represents hydrogen or a group of the formula -CH₂-OH or CH₂O-CO-R¹²,
- in which
- 25 R¹² denotes hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms or phenyl which is optionally substituted up to 3 times, identically or differently, by halogen, hydroxyl, cyano or straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,
- 30 or of the general formula (A4)



in which

5 A represents a radical of the formula



in which

10 R³, R⁴, R⁶ and R⁷ are identical or different and

denote hydrogen, cycloalkyl having 3 to 7 carbon atoms or aryl
having 6 to 10 carbon atoms,

15 or denote straight-chain or branched alkyl or alkenyl each
having up to 8 carbon atoms, each of which is optionally
substituted by halogen, hydroxyl or aryl having 6 to 10 carbon
atoms,

T, V, X and Y are identical or different and denote an oxygen or
20 sulphur atom,

25 R⁵ and R⁸ are identical or different and
denote hydrogen, halogen, cycloalkyl having 3 to 8 carbon
atoms or straight-chain or branched alkyl or alkenyl each
having up to 8 carbon atoms, each of which is optionally

substituted by cycloalkyl having 3 to 8 carbon atoms, or by a 5-
to 6-membered, aromatic, optionally benzo-fused heterocycle
having up to 3 heteroatoms from the group consisting of S, N
and/or O, or by aryl having 6 to 10 carbon atoms, where the
cyclic systems for their part can be substituted up to 3 times,
identically or differently, by a 5- to 6-membered aromatic
heterocycle having up to 3 heteroatoms from the group
consisting of S, N and/or O, or by phenyl, benzyl, halogen,
hydroxyl, carboxyl or by straight-chain or branched alkyl,
alkoxy or alkoxy carbonyl each having up to 6 carbon atoms, or
denote aryl having 6 to 10 carbon atoms or a 5- to 7-membered
aromatic, optionally benzo-fused heterocycle having up to 3
heteroatoms from the group consisting of S, N and/or O, each
of which is optionally substituted up to 3 times, identically or
differently, by halogen, phenyl, trifluoromethyl, hydroxyl,
carboxyl or by straight-chain or branched alkyl, alkoxy or
aloxycarbonyl each having up to 6 carbon atoms or by a group
of the formula -(CO)_a-NR⁹R¹⁰,

in which

a denotes a number 0 or 1,

R⁹ and R¹⁰ are identical or different and
denote hydrogen, phenyl or straight-chain or branched
alkyl or acyl each having up to 5 carbon atoms,

D and E are identical or different and
represent hydrogen, halogen, trifluoromethyl, hydroxyl, carboxyl or
straight-chain or branched alkyl, alkoxy or aloxycarbonyl each
having up to 6 carbon atoms,

- 5 R¹ represents hydrogen or cycloalkyl having 3 to 8 carbon atoms, or
 represents straight-chain or branched alkyl or alkenyl each having up
 to 8 carbon atoms, each of which is optionally substituted by
 cycloalkyl having 3 to 6 carbon atoms, phenyl or by a 5- to
 6-membered aromatic heterocycle having up to 3 heteroatoms from
 the group consisting of S, N and/or O, or
 represents phenyl or a 5- to 6-membered aromatic heterocycle having
 up to 3 heteroatoms from the group consisting of S, N and/or O, the
 ring systems optionally being substituted up to 3 times, identically or
 differently, by halogen, phenyl, trifluoromethyl or straight-chain or
 branched alkyl or alkoxy each having up to 5 carbon atoms, hydroxyl
 or by a group of the formula -NR¹¹R¹²,
- 10 15 in which
- R¹¹ and R¹² have the meaning of R⁹ and R¹⁰ indicated above and
 are identical to or different from this,
- 20 L represents an oxygen or sulphur atom,
- R² represents mercapto, hydroxyl, straight-chain or branched alkoxy
 having up to 8 carbon atoms or the group of the formula
- 25
$$\begin{array}{c} \text{R}^{14} \\ | \\ -\text{N}\text{R}^{13}-\text{C}-\text{H}-\text{R}^{15} \end{array},$$

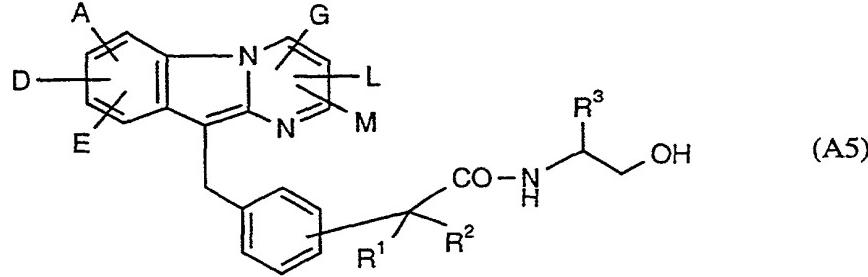
 in which
- R¹³ denotes hydrogen or straight-chain or branched alkyl having up

to 4 carbon atoms,

5 R¹⁴ denotes hydrogen, phenyl or a 5- to 6-membered aromatic heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O,

10 R¹⁵ denotes hydrogen or straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by hydroxyl,

15 or of the general formula (A5)



in which

15 A, D, E, G, L and M are identical or different and represent hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl, straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

20 R¹ and R² are identical or different and represent hydrogen, cycloalkyl having 3 to 8 carbon atoms or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms or

represent phenyl which is optionally substituted by halogen or trifluoromethyl, or

5 R¹ and R², together with the carbon atom, form a 4- to 8-membered cycloalkyl ring

and

10 R³ represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxycarbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,
15 and/or is optionally substituted by a group of the formula -OR⁴ or -NR⁵R⁶,

in which

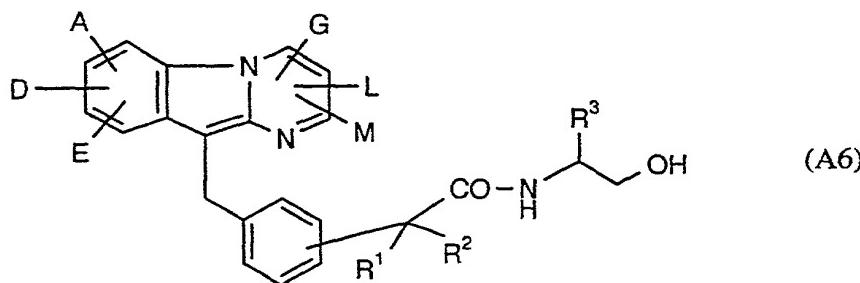
20 R⁴ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

25 R⁵ and R⁶ are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, or denote straight-chain or branched acyl having up to 8 carbon atoms, which is optionally substituted by a group of the formula -NR⁷R⁸,

30 in which

R^7 and R^8 are identical or different and
denote hydrogen or straight-chain or branched acyl
having up to 8 carbon atoms,

5 or of the general formula (A6)



in which

10 A, D, E, G, L and M are identical or different and
represent hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl,
straight-chain or branched alkoxy or alkoxy carbonyl each having up to
6 carbon atoms or straight-chain or branched alkyl having up to
6 carbon atoms, which for its part can be substituted by hydroxyl or by
15 straight-chain or branched alkoxy having up to 4 carbon atoms,

R¹ and R² are identical or different and
represent hydrogen, cycloalkyl having 3 to 8 carbon atoms or straight-
chain or branched alkyl having up to 10 carbon atoms, which is
20 optionally substituted by cycloalkyl having 3 to 6 carbon atoms, or
represent phenyl which is optionally substituted by halogen or
trifluoromethyl, or

25 R¹ and R², together with the carbon atom, form a 4- to 8-membered
cycloalkyl ring

and

5 R³ represents phenyl which is optionally substituted up to 3 times, identically or differently, by nitro, carboxyl, halogen, cyano or by straight-chain or branched alkenyl or alkoxy carbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,
10 and/or is optionally substituted by a group of the formula -OR⁴ or -NR⁵R⁶,

in which

15 R⁴ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

20 R⁵ and R⁶ are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, or denote straight-chain or branched acyl having up to 8 carbon atoms, which is optionally substituted by a group of the formula -NR⁷R⁸,

in which

25 R⁷ and R⁸ are identical or different and denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

30 if appropriate in an isomeric form and their salts

- with HMG-CoA reductase inhibitors as component B for the production of medicaments for the prophylaxis and/or treatment of cardiovascular diseases.
2. Use of a combination according to Claim 1 for the production of medicaments for the control or prophylaxis of cardiovascular diseases which are associated with metabolic diseases or deficits.
- 5
3. Use of a combination according to Claim 2 for the control of arteriosclerosis, diseases of the coronary vessels of the heart, raised serum lipids, hypercholesterolaemia, hypertriglyceridaemia and mixed forms which are combined with raised VLDL or LDL and/or raised chylomicrons, and of syndrome X.
- 10
4. Use of a combination according to Claim 2 for the treatment of secondary hypercholesterolaemia and secondary hypertriglyceridaemia, which are optionally associated with apolipoprotein E polymorphism, obesity, chylomicronaemia and chylomicronaemia syndrome, renal insufficiency, chronic renal insufficiency, nephrotic syndrome, diabetes mellitus type II, and with hepatomas and plasmacytomas.
- 15
5. Use of a combination according to Claim 2, characterized in that it contains, as component A, a compound of the general formula (A1).
- 20
6. Use of a combination according to Claim 2, characterized in that it contains, as component A, a compound of Examples 1-119.
- 25
7. Use of a combination according to Claim 2, characterized in that it contains, as component A, a compound of Examples 92-119.
- 30
8. Use of a combination according to Claim 2, characterized in that it contains, as component A, a compound of Examples 48 or 80.

9. Medicament comprising a combination of an MTP inhibitor as component A and an HMG-CoA reductase inhibitor as component B according to Claim 1 and, if appropriate, one or more further suitable components.
- 5
10. Medicament according to Claim 9, characterized in that it contains, as component A, the active compound 2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide or 2-cyclopentyl-2-[4-(2,4-dimethyl-pyrimido[1,2-a]indol-10-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide and, as component B, the active compound atorvastatin, cerivastatin, simvastatin, pravastatin, lovastatin, fluvastatin, itavastatin or ZD 4522.
- 10
11. Medicament according to Claim 9, characterized in that it contains, as component A, the compound (2S)-2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-ylmethyl)-phenyl]-N-(2-(1R)-hydroxy-1-phenyl-ethyl)-acetamide.
- 15
12. Process for the production of medicaments according to Claim 9, characterized in that the components A and B are converted into a suitable administration form with excipients and vehicles and, if appropriate, with further components.
- 20

COMBINED DECLARATION AND POWER OF ATTORNEY

ATTORNEY DOCKET NO

Le A 33 846

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought

on the invention entitled

**COMBINATION OF MTP INHIBITORS AND HMG-CoA REDUCTASE INHIBITORS
AND THE USE THEREOF IN MEDICAMENTS**

the specification of which is attached hereto,

or was filed on June 13, 2000

as a PCT Application Serial No. PCT/EP00/05410

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s), the priority(ies) of which is/are to be claimed:

199 29 065.2	Germany	June 25, 1999
(Number)	(Country)	(Month/Day/Year Filed)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose the material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

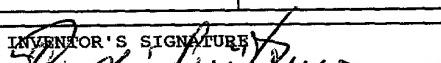
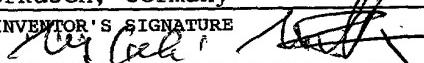
Le A 33 846-US

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Jeffrey M. Greenman, Reg. No. 26,552
Barbara A. Shime, Reg. No. 29,862
William F. Gray, Reg. No. 31,018
Alice A. Brewer, Reg. No. 32,888
Jerrie L. Chiu, Reg. No. 41,670
Susan M. Pellegrino, Reg. No. 48,972

Susan M. Pellegrino, Reg. No. 48,972

all of Bayer Corporation, 400 Morgan Lane, West Haven, Connecticut 06516

Send Correspondence To: <u>Mr. Jeffrey M. Greenman</u> <u>Bayer Corporation</u> <u>400 Morgan Lane</u> <u>West Haven, Connecticut 06516</u>		Direct Telephone Calls To: (203)812-3964(Jerrie L. Chiu)	
FULL NAME OF SOLE OR FIRST INVENTOR <u>Rudi Grützmann</u>		INVENTOR'S SIGNATURE 	DATE <u>5.12.01</u>
RESIDENCE D 42657 Solingen, Germany <u>DEX</u>		CITIZENSHIP German	
POST OFFICE ADDRESS c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany			
FULL NAME OF SECOND INVENTOR <u>Ulrich Müller</u>		INVENTOR'S SIGNATURE 	DATE <u>5.12.2001</u>
RESIDENCE D 42111 Wuppertal, Germany <u>DEX</u>		CITIZENSHIP German	
POST OFFICE ADDRESS c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany			
FULL NAME OF THIRD INVENTOR <u>Hilmar Bischoff</u>		INVENTOR'S SIGNATURE 	DATE <u>29.11.01</u>
RESIDENCE D 42113 Wuppertal, Germany <u>DEX</u>		CITIZENSHIP German	
POST OFFICE ADDRESS c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany			
FULL NAME OF FOURTH INVENTOR		INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
FULL NAME OF FIFTH INVENTOR		INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
FULL NAME OF SIXTH INVENTOR		INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			
FULL NAME OF SEVENTH INVENTOR		INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP	
POST OFFICE ADDRESS			